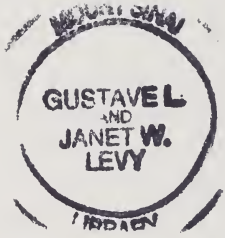
THE
MOUNT
SINAI
LIBRARY


GUSTAVE L.
AND
JANET W.
LEVY

GUSTAVE L.
AND
JANET W.
LEVY

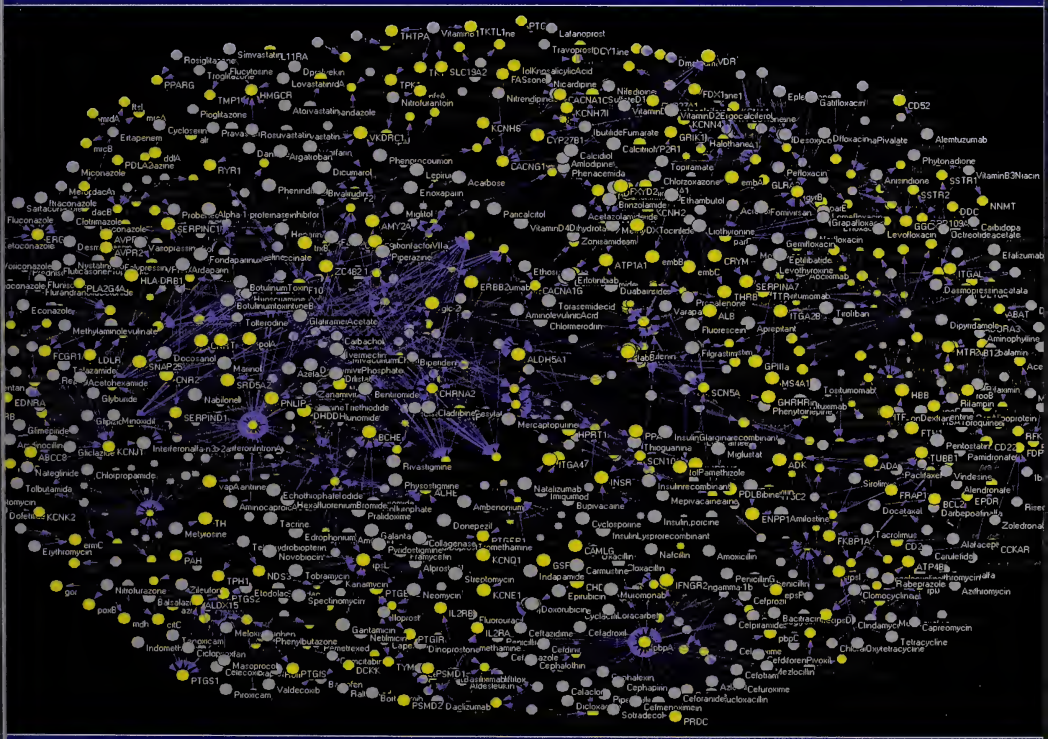
Digitized by the Internet Archive
in 2015

https://archive.org/details/mountsinaijourna7412moun

VOL. 74, NO. 1
APRIL 2007

MOUNT SINAI JOURNAL OF MEDICINE

A Journal of Translational and Personalized Medicine



IN THIS ISSUE

The Journal: A Retrospective

Translational Experimental Therapeutics

Pathology in Translational and Personalized Medicine

BICENTENNIAL 1807 WILEY 2007 BICENTENNIAL

Discover Something Great

Distinctive Content

Content
Journals • Backfile Collections
Reference Works & Encyclopedias
OnlineBooks™
Current Protocols Lab Manuals
Evidence-Based Resources

Access
Single article/chapter or full title
One-time fee, subscription,
or Pay-Per-View options
Unlimited concurrent usage

Capabilities
E-mail Alerts • EarlyView®
Citation download & tracking
Remote access • Mobile Edition®

Promote the process of scientific discovery with a different breed of research system: **Wiley InterScience®**. Long distinguished by its scope and extensive coverage of emerging disciplines, Wiley's authoritative content spans the spectrum of scientific, medical, technical, and business specialties. The dynamic **Wiley InterScience** platform adds value to your research by providing simple desktop access to this preeminent digital library of journals, reference works, books, laboratory manuals, evidence-based databases, and more. Researchers reap the combined benefits of top-tier resources and up-to-the-minute functionality. Experience the difference **Wiley InterScience** can make at your institution today.

WILEY InterScience®
DISCOVER SOMETHING GREAT

WILEY
1807-2007 KNOWLEDGE FOR GENERATIONS

www.interscience.wiley.com

MOUNT SINAI JOURNAL OF MEDICINE

A JOURNAL OF TRANSLATIONAL AND PERSONALIZED MEDICINE

CONTENTS
VOL 74, NO 1

1 Old, Yet Ever New
Penny A. Asbell

2 The Journal: A Retrospective
Barbara J. Niss and Arthur H. Aufses

7 Translational Experimental Therapeutics: The Translation of Laboratory-Based Discovery into Disease-Related Therapy
Karl Kieburtz and C. Warren Olanow

15 Foundations, Promises and Uncertainties of Personalized Medicine
Erwin P. Bottinger

22 The Role of the Pathologist in Translational and Personalized Medicine
Daniel P. Perl

27 Network Analysis of FDA Approved Drugs and their Targets
Avi Ma'ayan, Sherry L. Jenkins, Joseph Goldfarb and Ravi Iyengar

33 Handwashing and Infection Control
Fred Rosner

36 Job of the Bible: Leprosy or Scabies?
Thierry Appelboom, Elie Cogan and Jean Klastersky

40 Apparent Mineralocorticoid Excess Manifested in an Elderly Patient with Hypothyroidism
Maria I. New

On the Cover: A network map of the FDA approved drugs and their protein targets in human cells. The image represents a bipartite network of interactions between drugs and their human gene products. The information about these interactions was obtained from the FDA Electronic Orange Book (EOB) and DrugBank. Gray nodes represent drugs and yellow nodes their known human protein targets (Entrez Gene names). The network contains one large cluster that is enriched in drugs that target G protein coupled receptors. A high-resolution image can be viewed at www.mssm.edu/labs/iyengar.

The Wiley Bicentennial–Knowledge for Generations

Each generation has its unique needs and aspirations. When Charles Wiley first opened his small printing shop in lower Manhattan in 1807, it was a generation of boundless potential searching for an identity. And we were there, helping to define a new American literary tradition. Over half a century later, in the midst of the Second Industrial Revolution, it was a generation focused on building the future. Once again, we were there, supplying the critical scientific, technical, and engineering knowledge that helped frame the world. Throughout the 20th Century, and into the new millennium, nations began to reach out beyond their own borders and a new international community was born. Wiley was there, expanding its operations around the world to enable a global exchange of ideas, opinions, and know-how.

For 200 years, Wiley has been an integral part of each generation's journey, enabling the flow of information and understanding necessary to meet their needs and fulfill their aspirations. Today, bold new technologies are changing the way we live and learn. Wiley will be there, providing you the must-have knowledge you need to imagine new worlds, new possibilities, and new opportunities.

Generations come and go, but you can always count on Wiley to provide you the knowledge you need, when and where you need it!

William J. Pesce

William J. Pesce
President and Chief Executive Officer

Peter Booth Wiley

Peter Booth Wiley
Chairman of the Board

MOUNT SINAI JOURNAL OF MEDICINE

A JOURNAL OF TRANSLATIONAL AND PERSONALIZED MEDICINE

Editor
Penny A. Asbell

Deputy Editors
Dennis Charney

Maria New

C. Warren Olanow

Editorial Board
Stuart Aaronson
Erwin Bottinger
Mark R. Chassin
Eric Hollander
Ravi Iyengar
Paul Klotman
Mary Klotman
Fred Lublin
Thomas G. McGinn
Susan Morgello
Hugh Sampson
Mary Sano
Fred Suchy
Anthony Squire
Savio Woo

Mount Sinai School of Medicine
New York, New York.

Journal Publisher
Jennifer English
Senior Editor
John Wiley & Sons
jenglish@wiley.com

MOUNT SINAI JOURNAL OF MEDICINE

A JOURNAL OF TRANSLATIONAL AND PERSONALIZED MEDICINE

©**2007 Mount Sinai School of Medicine.** All rights reserved. No part of this publication may be reproduced in any form or by any means, except as permitted under section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the publisher, or authorization through the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, Phone: (978) 7S0-8400; Fax: (978) 7S0-4770. Such requests and other permission inquiries should be addressed to the Permissions Department, c/o John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030; Phone: (201) 748-6011; Fax: (201) 748-6008; E-mail: permreq@wiley.com.

Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine (Print ISSN: 0027-2507; Online ISSN: 1931-7S81 at Wiley InterScience, www.interscience.wiley.com) is published six times per year in April, June, August, September, November, and December for the Mount Sinai School of Medicine by Wiley Subscription Services, a Wiley Company, 111 River Street, Hoboken, NJ 07030.

Send subscription inquiries to: Subscription Department, c/o John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030; (201) 748-664S.

Offprint sales and inquiries should be addressed to the Reprint Billing Department, c/o John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030; (201) 748-8776. All other inquiries should be addressed to the Customer Service Department at (201) 748-664S.

Individual subscription price: $95.00 in North America, $120.00 outside North America. Payment must be made in US dollars drawn on a US bank. Claims for undelivered copies will be accepted only after the following issue has been delivered. For more subscription prices and information, please visit www.mountsinaijournal.org.

Change of address: Please forward six weeks prior to move: present mailing label with change of address. Please enclose a copy of the mailing label or cite your subscriber reference number in order to expedite handling. Missing copies will be supplied when losses have been sustained in transit and where reserve stock permits. Send claims in care of: *Mount Sinai Journal of Medicine*, c/o John Wiley & Sons, Inc., Attn: Journals Admin Dept. UK, 111 River Street, Hoboken, NJ 07030.

Cancellations: Subscription cancellations will not be accepted after the first issue has been mailed. Periodicals postage paid at Hoboken, NJ and at additional mailing offices.

Postmaster: Send address changes to *Mount Sinai Journal of Medicine*, Subscription Distribution, c/o John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030. Printed in the United States of America.

Advertising inquiries should be addressed to: Advertising Sales Manager, c/o John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030. Phone: (201) 748-6921; Fax: (201) 748-6207. Advertising in this journal is published with a caveat emptor understanding. The Publisher, Editors, and members of the Editorial Board do not imply warranty of products, nor quality, validity, or approval of education material offered by such advertising.

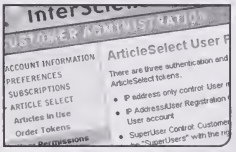
Indexed by: Biological Abstracts® (Thomson ISI), Chemical Abstracts Service/SciFinder (ACS), Current Contents®/Clinical Medicine (Thomson ISI), EMBASE/Excerpta Medica (Elsevier), Index Medicus/MEDLINE/PubMed (NLM), Science Citation Index Expanded™ (Thomson ISI), SCOPUS (Elsevier), Web of Science® (Thomson ISI).

This journal is printed on acid-free paper.

Disclaimer: All articles published, including but not limited to original research, reviews, clinical notes, clinical pearls, prismatic cases, clinician's corner, editorials, reports, and letters, represent the opinions and views of the authors and do not reflect any official policy or medical opinion of the Mount Sinai School of Medicine, the institutions with which the authors are affiliated, or the Publisher unless this is clearly specified. Articles published herein should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by physicians for any particular patient or disorder. Although the Editors and Publisher believe that drug selections and dosages and the specifications and usage of equipment and devices as set forth herein are in accord with current recommendations and practice at the time of publication, they accept no legal responsibility for any errors or omissions, and make no warranty, express or implied, with respect to material contained herein.

Why Wait to Make Great Discoveries?

When you can make them in an instant with Wiley InterScience® Pay-Per-View and ArticleSelect™ Tokens



Get instant, full-text access to the most distinguished collection of journals online books, reference works and encyclopedias or Current Protocols Laboratory Methods – all available on Wiley InterScience. With Pay-Per-View and ArticleSelect™, there's no limit to what you can discover...

ArticleSelect™ Tokens provide access to full-text content from journals, books and reference works outside of your institution's subscription holdings. Ask you library if it provides this service.

Pay-per-view is available to all users who wish to access an article immediately via a secure credit card transaction. Articles are available for $25.

Benefits:

- Access online full-text content from journals and books that are outside your current library holdings
- Get the information you need instantly no waiting for document delivery
- Use it at home, on the road, from anywhere at any time
- Access to purchased content is instant and lasts for up to 24 hours

WILEY
1807-2007 KNOWLEDGE FOR GENERATIONS

WILEY InterScience®
DISCOVER SOMETHING GREAT
www.interscience.wiley.com

EDITORIAL

Old, Yet Ever New

Penny A. Asbell, MD

Department of Opthalmology, Mount Sinai Medical Center, New York, New York

Communication is the key to success, whether you are a clinician in practice, a clinician scientist or laboratory-based researcher, or a patient hearing a diagnosis for the first time. Given the explosion in the amount of medical information and the revolutionary nature of some of that information, we all need methods to stay abreast not only in our areas of special interest but also outside of our specialties, in order to maintain our cutting-edge knowledge and to provide excellence in patient care, research and education.

This journal seeks to fill that need.

With this issue we are relaunching the *Mount Sinai Journal of Medicine* and dedicating it to improved communication among all participants in medicine today, with the hope that quality, in-depth review articles will allow all stakeholders–clinicians, teaching faculty, basic and clinical researchers–to integrate new information into their lives and utilize this information for new discoveries and new insights into patient care. To highlight this change in focus of the Journal, we have added a new subtitle: *A Journal of Translational and Personalized Medicine.*

What is translational medicine? The simple answer is research that goes from "bench to bedside and back again" to provide continuous feedback and improvements in understanding, diagnosing and treating human disease. Advances will depend on improving the pathway from understanding basic disease mechanisms to effective new treatments: "translational experimental therapeutics."

What is personalized medicine? With the advent of identification of the human genome there can be no doubt that each individual is unique and ultimately deserves a unique approach to diagnosis and treatment based on the individual's own genetic response to the environment and to treatment. The bar has been raised, and the challenge now is to find molecular markers that will enable doctors to prevent disease even before symptoms appear. This new approach holds great promise for fine-tuning patient care and ultimately for reducing healthcare costs. Translational and personalized medicine both profit from the use of modern information systems, which have made it possible to analyze and correlate massive databanks of heretofore unrelated information and given birth to the new field of systems biology and network sciences.

The Mount Sinai Journal of Medicine has a distinguished career, continuously publishing since 1934 and included in the Index Medicus from the very first volume. We aim now to build upon this tradition of education across medical specialties through presentation of medical research-based information with our new mission and new journal format to bring added value to all our readers and inspire the creative thinking needed to create new ways to understand, prevent and treat human disease.

"It is not the strongest of the species that survives, nor the most intelligent, but rather the one most responsive to change."–Charles Darwin

Address Correspondence to:

Penny A. Asbell
Department of Opthalmology
Mount Sinai Medical Center
1 Gustave Levy Place, Box 1183
New York, NY 10029
Email: penny.asbell@mssm.edu

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20004

© 2007 Mount Sinai School of Medicine

The Journal: A Retrospective

Barbara J. Niss, MA[1] and Arthur H. Aufses, Jr., MD[2]

[1]Mount Sinai Archivist, Levy Library, Mount Sinai Medical Center, New York, New York
[2]Professor of Surgery and Health Policy, Mount Sinai Medical Center, New York, New York

Abstract

With this issue, *The Mount Sinai Journal of Medicine* moves from being a general medical publication to one specializing in translational and personalized medicine. This article traces the history of *The Journal* from its beginning in 1934 to the present day. The Editors and their editorial policies are discussed, with mention of many articles over the years that have made the *Journal* truly a part of Mount Sinai's history. ***Mt Sinai J Med 74:2–6, 2007.*** © *2007 Mount Sinai School of Medicine*

Key Words: journalism, medical publishing periodicals mount sinai hospital.

This issue of *The Mount Sinai Journal of Medicine* represents a new beginning. However, each new beginning also marks the end of what went before, and so it is now appropriate to look back at the history of the *Journal*. As one of a very few institutionally based publications, the purpose and path of this publication have always been different from the mainstream.

To people who love the history of Mount Sinai, reading the Mount Sinai *Journal* is like looking through a scrapbook filled with old friends and memories. The *Journal* tells its tales of Mount Sinai in two different ways. First there are papers about Mount Sinai itself, with memoirs telling stories stretching back to the old Hospital on Lexington Avenue, because the *Journal* was founded at a time when people who knew the original "giants" were still around[1,2,3]. There is even a history of the Hospital as a whole, written for the 90th anniversary in 1942[4]. Then there are the scientific papers that have formed the main portion of the *Journal* over the years, its raison d'être. These show the state of research at Mount Sinai, the areas of interest of the staff, and how medicine and research were understood and practiced at each point in time.

The *Journal* did not set out to be historical documentation of Mount Sinai's path. It was born in 1934 as an outgrowth of what has been a continuing theme at Mount Sinai for over a century: the imperative that this institution should serve the community by being a place of learning and teaching. This theme was evident in the 1930s in the Clinical Pathological Conferences (CPCs) that were open to–and well attended by–the general medical public; in the post-graduate courses that were offered to outside physicians and put on a formal basis with Columbia University in 1923; and in the special lectures that were endowed to bring outside experts in both the basic sciences and clinical fields to the campus to speak. It is no coincidence that from the beginning of *The Journal of The Mount Sinai Hospital* in 1934, a portion of the content has been composed of those CPCs, presentations, and lectures. Under the aegis of the Hospital's Committee On Medical Education and Publications, the *Journal* was founded specifically to help share the knowledge that was created or delivered at Mount Sinai.

In 1940, the first Editor of the *Journal* wrote a (not surprisingly) brief history of the publication. That Editor was Joseph A. Globus, MD, a pioneer neuropathologist who joined Mount Sinai's staff in 1920 on a fellowship and spent his entire career here. He founded the neuropathology laboratory at Mount Sinai and performed ground-breaking work on brain tumors and their classification. Along with the Mount Sinai *Journal,* he was also founding editor of the *Journal of Neuropathology and Experimental Neurology* in 1942. In his 1940 review of the events leading up to the creation of the Mount Sinai publication, he wrote:

Address Correspondence to:

Barbara J. Niss
Box 1102
Mount Sinai Medical Center
1 Gustave L. Levy Place
New York, NY 10029-6574
Email: Barbara.Niss@mssm.edu

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20000

© 2007 Mount Sinai School of Medicine

> On March 15, 1934 the first number of the Journal was to appear, but I still had no subscribers, no material for the Journal and no definite arrangement for its publication. I communicated with members of the staff, alumni and friends of the hospital and an immediate response resulted in 580 subscribers to the Journal. . .. It was highly essential to get outstanding material for the first number of the Journal and the problem was fortunately solved when Dr. Callop [sic] delivered his Welch lectures. He was very anxious to have it published early and the Journal of the Mount Sinai Hospital was the only journal that could publish it so hurriedly. It was a Godsend to the Journal and insured success for the first number of the Journal[5].

That first issue set the tone of the *Journal* for the next two decades. Along with the Collip article, there were seven case reports, a memorial essay on the Mount Sinai surgeon, Alexis V. Moschcowitz, and one page of abstracts of articles by Mount Sinai authors published elsewhere. The issue included many types of illustrations, including x-rays, medical drawings, photographs, and slides. All of this could be had for the annual subscription price of $2. Mount Sinai's reputation was such, and the *Journal*'s quality substantial enough, that from its first volume, it was indexed in the *Index Medicus*, making information about its content available world-wide. By 1940, the paid circulation for the bi-monthly publication was 700, with an additional 250 being sent gratuitously to libraries around the world, with the exception, noted pointedly by the Editor, of Italy and Germany[5].

The *Journal* remained centered on clinical cases and lectures during the Globus years, but not exclusively so. Special issues devoted to eminent Mount Sinai physicians were published upon their retirement, the anniversary of their service at Mount Sinai, or death. These *festschrifts* often assumed the theme of their subjects' specialty: Bernard Sachs and neurology[6]; Edwin Beer and urology[7]; A.A. Berg and surgery[8]. The growing medical specialties were also represented by the inclusion of lectures in these fields, such as the Isidore Friesner Lecture in Otolaryngology, which, in 1951, was given by the respected otologist, Julius Lempert[9]. There were also memorial essays and obituaries published whenever Mount Sinai physicians, and some Trustees, died. Other types of articles appeared over these decades, ultimately making the *Journal* a general medical publication of broad interest to practicing physicians.

In 1952, Joseph Globus died. Although from the beginning, and to this day, there has always been an Editorial Board on which the Editor could lean, it has played a greater or lesser role depending on the people involved and the Editor. Many Mount Sinai physicians and scientists have served on the Boards over the years, but it is hard to document their exact role, especially since the *Journal* has always had strong Editors with confirmed opinions on their direction. Globus was certainly just the first in this mold. On the 50th anniversary of the *Journal*, Lester Tuchman wrote:

> Dr. Globus was the captain, the crew, and the bo'sun tight of our good ship Nancy Bell. It was his drive, his industry, his zeal, his good-hearted and never-misunderstood bluster which was the driving force of the *Journal*. Without Dr. Globus the *Journal* would never have survived[10].

But survive it did. Solon S. Bernstein, MD, from the Department of Medicine, was appointed the second Editor of the *Journal,* but he died suddenly of a brain tumor and only oversaw volume 20. Thus, in 1954, on the twentieth anniversary of the founding of the *Journal*, Lester R. Tuchman, MD, was promoted from the Editorial Board to be the third Editor, later becoming the longest serving Editor in *Journal* history. Over the next two decades, under Tuchman's leadership, the *Journal* evolved to match the changing medical landscape, as well as the changing Mount Sinai Hospital.

Tuchman, interestingly enough, served as House Surgeon while on the house staff at Mount Sinai. He later rose through the ranks in the Department of Medicine to become a full Attending and Director of Medicine at the Mount Sinai affiliated City Hospital Center at Elmhurst. Tuchman laid out his plans for the *Journal* in an editorial in 1954. He noted that "the major aim of the *Journal*, now as then, is to make available its pages for case reports based upon the extraordinary clinical material which our Hospital has always had, some of which might otherwise be lost." Tuchman, noted, however, that the editors now preferred that their authors "come from the ranks of the House and Resident Staffs, Fellows, and younger men generally[10]." To encourage these submissions, the Joseph H. Globus Memorial Prize was created for the best paper published by authors of Assistant Attending and lesser rank each year in the *Journal*. The first Prize was awarded in 1955 to Dr. Mortimer Ostow for his paper entitled, "Electrical response of the cerebral cortex to corticopital impulses: a comparison of peripheral and contralateral cortical stimulation[11]". A prize to encourage house staff contributions was created in 1957. The Ralph Colp Award was established by friends, colleagues and patients of Dr. Colp and submissions in Colp's own field of surgery were given preference. Two years later, another House Staff award was created, the Daniel Stats Memorial Prize.

Although Tuchman kept the focus of the *Journal* on case reports, several changes happened over

DOI:10.1002/MSJ

The Editors of *The Mount Sinai Journal of Medicine*, 1934–1974. From left to right: Joseph A. Globus, MD (1934–1952); Solon S. Bernstein, MD (1952–1953); and Lester R. Tuchman, MD (1954–1974).

these years. The practice of including CPCs ended as they declined in importance in the Hospital (although they later reappeared and disappeared again). A section called "Radiological Notes" was created, and the volumes grew in size. A series of special symposia issues on particular topics were produced, with some of these also published as monographs. These ranged from the first in 1956, *The Management of Tuberculosis*, edited by Irving Selikoff[12] to *The Approach to Diagnosis in Modern Neurology*, edited by Morris B. Bender[13]. The subject matter of articles marked a step into modernity with a piece on computers in biomedical research in 1965. Also in the 1960s, the pages of the *Journal* were first opened up for nonMount Sinai authors. By 1968, the *Journal* continued on a bi-monthly basis, printing nearly 2,000 copies and distributed to medical libraries around the world. In an article in *The Mount Sinai Hospital News*, the value of the *Journal* was summarized as being the encouragement of young authors to publish; allowing authors to use more graphics in their articles; and a quicker turn-around period, allowing material to appear in print faster[14].

The creation of the Mount Sinai School of Medicine in the 1960s had a tremendous impact on the *Journal*. Some of the early papers about the new medical school appeared in its pages[15]. When the School was formally dedicated in October 1968, the *Journal* published the speeches of the four Nobel Laureates who had been invited to mark the occasion. (Probably not the first Laureate papers to appear; some of the earlier Welch and Janeway Lecture recipients went on to win the Nobel Prize.) Medical students were also encouraged to publish their research here and a prize to honor the best of these student papers was later created. Also, as the School developed affiliations with area hospitals and the off-site faculty grew, the *Journal* pages were opened to a larger group of authors and readers. But the biggest impact occasioned by the creation of the school was the decision to change the name of the *Journal* from *The Journal of The Mount Sinai Hospital* to *The Mount Sinai Journal of Medicine*. This became effective with volume 37 in 1970.

After holding the Editorship for twenty years, Lester Tuchman stepped down in 1974, the 40th anniversary of the *Journal*. The Mount Sinai Hospital Medical Board passed a resolution in Tuchman's honor, noting "that the Medical Board of Mount Sinai Hospital record herein this expression of our undying gratitude to Dr. Tuchman, inscribing his name in these annals to make known for succeeding generations the quality and scope of his contribution to the preeminence of this institution[16]". Tuchman was succeeded as Editor by David A. Dreiling, MD, a surgeon and world renowned pancreatologist who had joined the Editorial Board in 1961. (Dreiling also edited the *American Journal of Gastroenterology*.) In his debut editorial, he stated that he "intends the Journal to participate in the educational program of the Medical Center, for the medical student body, the Hospital medical staff, and the postgraduate physicians. We hope the Journal will serve as a medium of exchange between basic scientist and clinician, between student and educator, between Medical Center and community, and finally between alumnus and Mount Sinai[16]."

Dreiling implemented two major changes during his editorship. In 1979, with the first number of volume 46, the *Journal* changed format and began to be printed at its more recent 8 1/2 by 11 inches size. Initially it had a blue masthead, but beginning with volume 51 in 1984, the *Journal* colors changed with each new year and volume. It was not until 1996 (volume 63) that there was a return to the traditional, and to us familiar, blue and white covers. The other big change implemented

DOI:10.1002/MSJ

by Dreiling was the effort in 1984 to "nationalize" the *Journal*. This involved the publication's affiliation with three institutions–Cedars-Sinai Medical Center, Los Angeles; Mount Sinai Medical Center, Chicago; and Mount Sinai Medical Center, Miami. Dreiling hoped that these affiliations would broaden the base, not only of subscribers, but also of possible authors and reviewers. His ultimate goal was to have enough material to publish monthly, a goal that was never quite reached, although more issues were produced over the next couple of years before settling back to six. The formal affiliations were also short-lived, as institutional priorities changed over time.

In 1990, Sherman Kupfer, MD was appointed Co-Editor with Dreiling, who was in ill health. Dreiling died the next year and Kupfer assumed the full Editorship. Kupfer was really a triple threat: a skilled clinician in renal medicine; a funded researcher in kidney disease; and a devoted educator who taught physiology to medical students and clinical skills to scores of house staff in the Department of Medicine. He headed Mount Sinai's Research Committee for many years, and served as Deputy Dean from 1973–1984.

In an article outlining his plans for the *Journal,* Kupfer reviewed the history to date and once again stated the belief that there was still a need for a general medical journal that could pull together information across a spectrum of research and practice, as well as such areas as health policy, ethics and community medicine. He promised to continue to include special lectures and symposia given at Mount Sinai, grand rounds, case reports, and theme issues. He hoped to introduce articles about new drugs and include features on autopsy studies and surgical pathological specimens, as well as abstracts of work done at Mount Sinai's Department of Medicine and at the affiliates. As before, Kupfer hoped that the *Journal* would attract young authors, medical students and house staff, who would like a place to publish their early works. He promised a responsive editorial staff, and a quick turnaround time for manuscripts[17].

Over the next twelve years, Kupfer and the Editorial Board lived up to their words. A new column, Dermatology Notes, was introduced. Most issues featured articles under the headings of Grand Rounds, General Articles, and some Case Reports and Book Reviews. Theme issues were popular, with medical ethics appearing frequently, reflecting its growing presence at Mount Sinai itself. A new occasional series called Classics in Medicine was begun in 1999. Kupfer was very attuned not only to the *Journal's* history, but Mount Sinai's as well. The first Classic article was a reprinting of James Collip's Welch Lecture from volume 1 in 1934[18]. The next were two articles by Mount Sinai authors published elsewhere in the 1930s that laid the groundwork for what became known as Crohn's disease[19,20]. Kupfer hoped that by reprinting articles such as these, he could bring them to the attention of current readers. He also felt that, since the *Journal* had been placed online starting with volume 64 in 1997, the inclusion of these articles would make them available to a much larger readership on the World Wide Web. As Kupfer noted in a 2000 editorial: "*The Journal* will continue to republish accounts of important contributions made by Mount Sinai staff, from its own archives as well as from other publications, particularly where hard copy access may be limited or difficult. I hope that our readers will find this useful[21]."

In 2003, Kupfer died, leaving the *Journal* in the hands of Associate Editors Leslie A. Kuhn, MD, and Philip S. Ledereich, MD. Kuhn, a member of the Division of Cardiology for many years, was named full Editor starting with the May 2005 issue, and has served as such through the end of 2006, completing

The Editors of *The Mount Sinai Journal of Medicine*, 1974–2006. From left to right: David A. Dreiling, MD (1974–1991); Sherman Kupfer, MD (1990–2003); and Leslie Kuhn, MD (2005–2006).

DOI:10.1002/MSJ

volume 73. At the end of its current life, the *Journal* was around 425 pages per volume, and cost $85 for an annual individual subscription.

Conclusion

After 72 years of publishing, what then has the Mount Sinai *Journal* accomplished? It was rarely the place for publication of original ground-breaking research, with the notable exception of Ezra Greenspan and Mack Fieber's work on combination chemotherapy for breast and ovarian cancer, which was rejected by the mainstream cancer journals[22]. But it was never the intention of the *Journal's* founders or Editors to produce such a publication. It was instead their goal to extend Mount Sinai's usefulness to the world by spreading the knowledge created or displayed at the institution to a broad audience, and in this they have succeeded. In his 1974 letter of resignation from the editorship, Lester Tuchman wrote to Fenton Schaffner, MD, then Chairman of the Committee on Medical Education and Publications, that "Foreign readership is impressive, as evidenced by the large numbers of reprint requests which come from scores of countries and from all continents. Members of our staff returning from the most remote and exotic countries, as well as from famous old centers, are continually astounded at the respect in which the *Journal* is held all over the world[23]." As Dreiling noted in 1984, on the Fiftieth anniversary of the *Journal*: "Our aim. . . above all [is] to make the Journal truly useful to all of our readers, and thus to serve medicine[24]." A noble goal, well fulfilled.

References

1. The Mount Sinai Hospital and its surgeons of the middle eighties: a few recollections. *J Mt Sinai Hosp N Y* 1937; 3: 229–240.
2. Elsberg CA. Mount Sinai in the late nineties and the beginning of neurosurgery in the hospital. *J Mt Sinai Hosp N Y* 1938; 4: 430–436.
3. Frank RT. Reminiscences, 1900–1937. *J Mt Sinai Hosp N Y* 1945; 12: 878–889.
4. The story of the Mount Sinai Hospital. *J Mt Sinai Hosp N Y* 1942–1943; v.8–10 passim.
5. "History of the Journal of the Mount Sinai Hospital," 7/2/40, in the Office of the Historian Files, Box 3, f.13, The Mount Sinai Archives.
6. *J Mt Sinai Hosp N Y* 1942; 9: 213–881.
7. *J Mt Sinai Hosp N Y* 1938; 4: 477–1091.
8. *J Mt Sinai Hosp N Y* 1951; 17: 351–1126.
9. Lempert J. Otology: Its present status. *J Mt Sinai Hosp N Y* 1952; 9: 381–395.
10. Tuchman LR. The Mount Sinai Journal: Past. *Mt Sinai J Med* 1984; 51: i–iv.
11. Ostow M. Electrical response of the cerebral cortex to corticopital impulses: a comparison of peripheral and contralateral cortical stimulation. *J Mt Sinai Hosp N Y* 1955; 21: 226–246.
12. Selikoff, Irving, Ed. *The management of tuberculosis.* New York: Waverly Press; 1956.
13. Bender, Morris B., Ed. *The approach to diagnosis in modern neurology.* New York: Grune & Stratton; 1967.
14. *The Mount Sinai Hospital News* April–May 1968; 60: 10.
15. Popper, Hans, Ed. *Trends in new medical schools.* New York: Grune & Stratton; 1967.
16. Editorial. *Mt Sinai J Med* 1974; 41: 609–614.
17. Kupfer S. The Journal 1990. *Mt Sinai J Med* 1990; 57: 1–2.
18. Collip JB. The William Henry Welch Lectures: Some recent advances in the physiology of the anterior pituitary. *Mt Sinai J of Med* 1999; 66: 343–364.
19. Ginzburg L, Oppenheimer GD. Non-specific granulomata of the intestine (inflammatory tumors and strictures of bowel). *Mt Sinai J of Med* 2000; 67: 246–262.
20. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. *Mt Sinai J of Med* 2000; 67: 263–268.
21. Kupfer S. Editor's note. *Mt Sinai J Med* 2000; 67: 245.
22. Greenspan EM, Fieber M. Combination chemotherapy of advanced ovarian carcinoma with the antimetabolite methotrexate and the alkylating agent thio-TEPA. *J Mt Sinai Hosp N Y* 1962; 29: 48–62; Greenspan EM, Fieber M, Lesnick G, and Edelman S. Response of advanced breast carcinoma to the combination of the antimetabolite methotrexate and the alkylating agent thio-TEPA. *J Mt Sinai Hosp NY* 1963; 30: 246–67.
23. Letter from Lester Tuchman to Fenton Schaffner, March 21, 1974 as reprinted in *Mt Sinai J Med* 1974; 41: 611.
24. Dreiling DA. The Mount Sinai Journal: Future. *Mt Sinai J Med* 1984; 51: v.

DOI:10.1002/MSJ

Translational Experimental Therapeutics: The Translation of Laboratory-Based Discovery into Disease-Related Therapy

Karl Kieburtz, MD[1] and C. Warren Olanow, MD[2]

[1]Professor of Neurology, University of Rochester Medical Center, Rochester, New York, New York
[2]Professor of Neurology and Neuroscience, Mount Sinai School of Medicine, New York, New York

Abstract

In the past decade, there has been an increasing emphasis on laboratory-based translational research. This has led to significant scientific advances in our understanding of disease mechanisms and in the development of novel approaches to therapy such as gene therapy, RNA interference, and stem cells. However, the translation of these remarkable scientific achievements into new and effective disease-modifying therapies has lagged behind these scientific accomplishments. We use the term "translational experimental therapeutics" to describe the pathway between the discovery of a basic disease mechanism or novel therapeutic approach and its translation into an effective treatment for patients with a specific disease. In this article, we review the components of this pathway, and discuss issues that might impede this process. Only by optimizing this pathway can we realize the full therapeutic potential of current scientific discoveries and translate the astounding advances that have been accomplished in the laboratory into effective treatments for our patients. ***Mt Sinai J Med 74:7–14, 2007.*** © *2007 Mount Sinai School of Medicine*

Key Words: experimental therapeutics, translational science, clinical trials.

Address Correspondence to:

Karl Kieburtz
Professor of Neurology
University of Rochester
Medical Center
1351 Mount Hope Avenue,
Suite 214
Rochester, NY 14620
Email: karl.kieburtz@ctcc.
rochester.edu

Introduction

During the past decade, there has been an exponential growth in translational bench research aimed at understanding the underlying nature of disease and developing novel forms of therapy.[1] This has led to major scientific accomplishments in diverse fields such as molecular genetics, cell biology and biochemical pathophysiology, and in the development of potentially revolutionary forms of treatment such as stem cells, gene therapy, and RNA interference. It is not surprising, therefore, that there is a high expectation for immediate therapeutic benefits in a wide range of disease states. Despite these scientific advances, the translation of bench research findings into clinically relevant treatments is neither simple nor assured. We have coined the term "translational experimental therapeutics" to describe the pathway of events between the initial laboratory discovery and the development of a new and approved therapy for a human disease (Table 1). This review will address the nature of this translational process, and touch on some of the potential issues and stumbling blocks that have limited our ability to translate positive research findings into effective therapies.

Preclinical Investigations

Discoveries relating to the etiology/pathogenesis of disease states and hypotheses for possible therapies based on these discoveries are frequently made at the level of *in vitro* model systems using cell and tissue preparations. The kinds of observations that can be made in these systems include disease- and treatment-related alterations in gene and protein expression, posttranscriptional protein modifications, perturbations in cell signaling

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20006

© 2007 Mount Sinai School of Medicine

Table 1. The Experimental Translational Therapeutic Pathway.

In vitro (single cell, cell culture) experiments to define mechanism and candidate interventions
↓
In vivo (whole animal) experiments to assess efficacy in relevant models
↓
Animal experiments for safety
↓
Drug activity studies
↓
IND application to the FDA (in the US)
↓
Initial human testing (Phase I)
↓
Exploratory (proof of concept) human efficacy and safety experiments (Phase II)
↓
Confirmatory human efficacy and safety experiments (Phase III)
↓
Effectiveness in medical practice (Postmarketing surveillance)

pathways (particularly those related to cell function, plasticity, survival, and death), and changes in the membrane-based receptor systems. These changes have the potential to provide new targets for the development of novel therapeutic interventions. Once a potential pathogenic mechanism has been identified, experiments can be designed to examine novel drugs or therapeutic strategies that might interfere with these pathologic processes. Again, such experimentation is often initially performed in relatively simple *in vitro* tissue culture model systems. How these cell and tissue culture studies relate directly to human disease, however, remains a matter of some conjecture.

Following sufficient replication to warrant faith in the reliability of the *in vitro* observations, the next logical step is to examine these observations in more complex systems such as animal models of the disease. The closer the animal model reflects the pathophysiology of the human disease, the more likely the model is to be predictive of the human response to an intervention. Rodent and canine species have been commonly used to try and replicate human pathophysiology and to test putative therapeutic interventions. They have been particularly valuable for testing models of diseases related to acute and chronic toxic exposure (e.g. smoking, air pollution, carcinogens).[2] Smaller animals such as nematodes and drosophila are also now widely used, and although more remote from the human condition, they permit high throughput and economical study of the molecular pathways involved in disease pathogenesis, identification of new targets for candidate drugs, and effects of new treatments.[3,4] The nonhuman primate is the laboratory model that most closely resembles the human, but experimentation is limited, owing to the cost and availability of these animals. Primates are typically used to address the more mature research questions (i.e. after they have been tested in lower animals) or those, which cannot be answered in lower animals. The choice of an animal model for a disease may be influenced by species-specific factors. For example, HIV infection is unique to humans, and animal models are based on the use of similar, but not identical, agents (e.g. simian immunodeficiency virus, feline immunodeficiency virus). Similarly, the toxin MPTP causes a Parkinson's disease-like syndrome in mice and monkeys, but not in rats. The development of transgenic mouse models that carry a mutation known to cause or act as a predisposing factor for a human genetic disorder has been an enormous step forward in developing animal models that have a closer etiopathogenic link to a human disease.[5–7] Interestingly, the transgenic animal models created for human neurodegenerative diseases such as Huntington's disease (R6/2 mice), amyotrophic lateral sclerosis (SOD mutant), Parkinson's disease (Parkin, alpha synuclein, LRRK2 mutations), and Alzheimer's disease (APP mutation) do not precisely model the human disease, nor have they been shown to accurately predict the human response to a disease modifying intervention.[8–12] While animal models are often of great value in predicting human response, these data illustrate that the same pathogenic agent may cause a different disease or even no disease in a different species, illustrating the difficulty in precisely and predictably translating results from animal models to humans.

Safety is an important consideration that must be addressed at the preclinical stage, before beginning human trials. Most academic-based researchers focus on creating a compelling scientific basis for a proposed intervention. However, for translational

DOI:10.1002/MSJ

experimental therapeutics and the introduction of a new agent into humans, the establishment of the safety profile of the proposed intervention is paramount. While pharmaceutical companies and those interested in regulatory requirements frequently have extensive experience in conducting the standard preclinical toxicologic, genotoxic, mutagenic and teratogenic experiments, academic researchers often have little experience in creating the necessary animal safety database needed to support human experimentation. Paradoxically, the US Food and Drug Administration (FDA) and the European regulatory authorities (via the International Conference on Harmonization [ICH]) have fairly standard guidelines for the animal safety data that is required prior to human experimentation, but they have no requirements for the amount of scientific evidence that must be obtained prior to proceeding with the study of a new intervention in humans.[13] This dichotomy between the data supporting a scientific rationale and the data supporting safety is a frequent stumbling block in taking a novel intervention from animal to human experimentation. Some relevant guidance documents from the FDA web site, agreed as part of the ICH process, are listed in Table 2.

Table 2. Guidance Documents Regarding Animal Safety Data Needed to Conduct Human Investigations.

M3	Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals	July 1997
S7A	Safety pharmacology studies for human pharmaceuticals	July 2001
S4	Guidance on the duration of chronic toxicity testing in animals	June 1999
S3A	Toxicokinetics: The assessment of systemic exposure in toxicity studies	March 1995
S2B	Genotoxicity: A standard battery for genotoxicity testing of pharmaceuticals	July 1997
S5A	Detection of toxicity to reproduction for medicinal products	Sept 1994
S1A	The need for long-term rodent carcinogenicity studies of pharmaceuticals	March 1996

These documents can be obtained at the FDA web site (www.fda.gov) by going to the Guidance page and searching for the specific documents.

Drug Activity: Getting Ready for Clinical Trials

When an intervention has been identified as a potential therapy, it is important to perform traditional measures of drug activity such as absorption, distribution, elimination, and metabolism prior to clinical testing for its safety and efficacy in humans. Information regarding how much of a drug is absorbed, by which route of administration (oral, intravenous, subcutaneous), to what degree it is protein bound and displaced by competing agents, to which tissue it is delivered and at what concentration, how it is metabolized, identification of active or toxic metabolites, route of elimination (renal, respiratory, fecal, skin), and potential to interfere with metabolism of other drugs are all important steps in characterizing a new drug prior to initiating clinical trials in humans. In addition, a very important consideration is whether the compound can exert its proposed mechanism of action at concentrations that are achievable in humans. For example, it is important to know that a putative monoamine oxidase (MAO) inhibitor for the treatment of Parkinson's disease reaches the brain in its anticipated active form and in sufficient concentration to accomplish its intended mechanism of action (i.e. inhibit MAO in the brain). In this regard, it is important to appreciate that some drugs have U-shaped curves, whereby they are effective within a limited range of concentrations, but are ineffective at higher or lower levels. In selecting a dose for human studies, it is important to appreciate that plasma concentrations may not provide an accurate measure of the drug concentration at the intended target site, that effective concentrations in one species may not be effective in another species, and that drug metabolism and transport may vary across species. Thus, selecting the correct dose for a given human trial may be difficult, and a full-range dosing study in both animal models and humans is usually required to define ineffective, effective, and toxic doses. The central nervous system presents unique considerations, as nonlipophillic agents do not passively cross the blood–brain barrier, and active transport systems that carry drugs both into and out of the brain may dramatically alter drug concentrations in the brain.[14] These measures of drug activity should ideally be well characterized prior to the use of a new intervention in human experiments.

A high proportion of potential therapeutic compounds will fail to transition to human study because of safety issues encountered in animal testing, as well as unanticipated problems with bioavailability and elimination. Particular areas of concern are inhibition of the cytochrome P450 enzyme system, which can alter the metabolism of many other drugs,[15,16] prolongation of cardiac repolarization resulting in long QT intervals, and an increased risk of arrythmia (US

DOI:10.1002/MSJ

Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CEDR), Center for Biologics Evaluation and Research (CBER). Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs. ICH of technical requirements for registration of pharmaceuticals for human use (ICH), October 2005)[17] and impairment of renal function.[18] The challenges in assembling sufficient preclinical evidence to support the rationale for human testing, as well as the challenges of generating adequate preclinical safety data have been recognized by the NIH Roadmap, an initiative to reengineer the clinical research and drug development process.[19,20] The NIH RAID pilot program (www.nihroadmap.nih.gov/raid) is specifically designed to help the investigators generate the animal toxicology data that are necessary to support human investigation. Resources are also available through this program to help with the production of sufficient quantities of drugs or other interventions according to good manufacturing practices (GMP). Laboratory evaluations are often performed with chemical (research) grade interventions. The manufacturing regulations surrounding the creation of drugs for testing in human patients is much more stringent, and governed by FDA regulations according to chemistry, manufacturing, and composition criteria (CMC). The transition from the manufacture of a chemical grade to a drug grade intervention can be costly and complicated. If there is no pharmaceutical manufacturer to assist with this process, academic investigators have few resources to draw on aside from the RAID program or NIH specific initiatives. There are other issues surrounding the manufacture of a drug, including the determination of which excipient should be employed along with the active agent (an excipient is an inert substance, which is added to a drug to provide bulk, for example in tablets), and whether the intervention should be administered as a pill, capsule, powder or injection. Frequently, the formulation used in preclinical disease models is different from that employed in human experiments, and may account for different safety and efficacy responses in human clinical trials in comparison with animal studies.

Clinical Trials

There is surprisingly little agreement within the scientific community about what preclinical evidence provides a satisfactory scientific rationale and justification for transitioning from animal to human experimentation. Scientists, clinicians, and ethicists debate the magnitude of change, the degree of specificity of the effect, and the level of safety that needs to be established before proposing experimental interventions in humans. Some researchers have proposed that benefits with a new intervention must be demonstrated in at least two different animal models before beginning human experimentation. It should be appreciated, however, that for many diseases there is no good animal model and safety and efficacy can only be properly assessed in patients with the target disease. These deliberations underscore the uncertainty of the predictive value of observations in animal models.[21] There is also a debate as to how often studies should be replicated by independent laboratories. It is an interesting fact that when initial observations are replicated, confirming laboratories tend to find a less robust effect of a putative intervention,[1] and when nonconfirmatory results are obtained, they are frequently not published by the investigator or are not accepted for publication by the major journals. This publication bias against nonconfirmatory replication may be a significant stumbling block in determining which mechanisms and interventions are most worthy of further investigation, and can lead to human subjects being unnecessarily exposed to a new agent that has not been adequately demonstrated to be effective or safe in the laboratory.

When the hurdles of establishing a scientific rationale and therapeutic effect in preclinical disease models, animal toxicology, drug manufacture, and dosing have been overcome, an intervention can make the transition from animal to human experimentation. In the United States, this transition can only be made after the satisfactory completion of an investigational new drug (IND) exemption application to the FDA. (CDER and CBER. Guidance for Industry: Content and format of IND applications for Phase 1 studies of drugs, including well-characterized, therapeutic, and biotechnology-derived products, November 1995). As part of the IND process, investigators must describe the planned clinical protocol and review how they have addressed issues such as toxicology/safety, drug activity, and drug manufacture. Most INDs are submitted by an industrial sponsor, but individual investigators can independently request an IND. Individuals who wish to submit an IND for the first time should seek advice from an experienced investigator who has already gone through this process. The FDA will meet in person with the applicant and will assist with the investigator-initiated IND application. Once the IND has been submitted, the FDA will provide feedback within a statutory timeframe regarding any perceived

DOI:10.1002/MSJ

deficiencies in the data submitted to support human experimentation.

All studies performed on human subjects must be approved by an Institutional Review Board (IRB) comprised of physicians, scientists, and lay members prior to their initiation. The IRB assures that there is equitable selection of subjects, potential risks are minimized, the risk benefit ratio is reasonable, and the informed consent fully describes in layman's language the possible risks and benefits of the procedure and any conflict of interest for the investigator or the institution. Additional review may be imposed for high-risk interventions such as gene therapy (must be approved by the recombinant advisory committee (RAC) of the FDA) and vulnerable populations such as children (must be approved by a special federal IRB that reviews high-risk pediatric research). All patients must understand the full details of the procedure and sign an IRB-approved informed consent before any aspect of the human study can be initiated.

Phase I Clinical Trials

Initial human experimentation, also referred to as Phase I or Human Pharmacology testing, is usually performed in healthy volunteers, but can, in some circumstances (for example with oncologic drugs), be conducted in individuals with the target disease process.[13] Initial Phase I testing is usually done in a highly controlled environment such as an inpatient clinical research center, and usually involves single dose exposure of the intervention to a limited number of individuals with intensive monitoring of safety and pharmacokinetic data (Table 3). Dosing for human trials is typically based on an extrapolation from doses that are effective and tolerated in animals,[22] and is an inexact science. Several steps are taken to introduce a safety margin for initial human dosing. Safety and tolerability of a single low dose is initially performed in small cohorts of individuals (usually 6–10 subjects). Thereafter, the dosage is gradually titrated upwards to a level that is not tolerated or induces side effects. This single dose paradigm is usually followed by a multiple dose study, typically 1 week in duration. Again, intensive safety monitoring and pharmacokinetics, particularly with doses that provide the maximal concentration of drug exposure (Cmax), must be a part of these investigations. The importance of careful monitoring during Phase I studies is illustrated by the recent experience with TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells.[23] Within 90 minutes of receiving a single intravenous dose of the drug, six volunteers developed a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines. They became critically ill with hypotension, pulmonary infiltrates, renal failure, and disseminated intravascular coagulation. Fortunately, the subjects had been closely monitored, effective interventions could be made, and there were no fatalities. Depending on the target population for the intervention, further Phase I study may also need to be done in healthy elderly populations or in those with renal or hepatic impairment.

Phase II clinical trials

If the accumulated safety and laboratory data in Phase I support further human investigations, Phase II or Therapeutic Exploratory testing (Proof of Concept Study) is conducted in the target disease patient population to provide a further assessment of safety as well as potential efficacy across a range of doses. Most Phase II studies are performed as multicenter, double blind, and placebo-controlled trials. These studies typically involve dozens to hundreds of subjects followed for 1–3 months. Careful evaluations of safety and accepted measures of disease activity based on clinical and laboratory examination are a standard part of Phase II testing. There is also a concerted effort to identify nonclinical markers of disease activity (e.g. biomarkers) that could be used to track the therapeutic response to the new intervention. Less intensive monitoring of pharmacokinetics is usually done in Phase II. In some fields such as oncology, it has become traditional to perform Phase II studies in an open-label manner and to compare the study results with historical measures of disease progression and toxicity. Blinding and contemporaneous control groups are, however, preferred whenever possible. Subjects who participate in Phase II studies are typically followed in an open-label extension phase in order to provide long-term safety data. Issues that must be considered in Phase II studies include the manufacture of matching placebo (made according to GMP regulations), the complexities of managing a large scale, multisite trial, and regulatory reporting requirements, particularly with respect to adverse effects. Contract Research Organizations are often employed to aid with study oversight, site monitoring, and database management. Investigative teams typically include clinical and basic researchers, biostatisticians, database managers, study monitors, and clinical trialists with a particular interest in the disease and in the management of clinical research studies.

DOI:10.1002/MSJ

Table 3. Stage of Human Clinical Trials.

Stage	Purpose	Subjects
Phase I	Tolerability	Healthy controls
Human pharmacology	Safety	(Tens)
	Pharmacokinetics	
Phase II	Explore efficacy in disease states	Patients
Therapeutic exploratory	Additional safety	(Dozens)
	Evaluate dose-response	
Phase III	Demonstrate efficacy	Patients
Therapeutic confirmatory	Establish safety	(Hundreds–thousands)
Phase IV	Refine dosing	Patients
Therapeutic use	Identify less common side effects	(Thousands)
	Identify new indications	Hundreds–thousands

Phase III clinical trials

The vast majority of compounds tested in Phase I and II studies fail to progress to Phase III testing because of safety concerns, lack of efficacy, or both. Phase III, or Therapeutic Confirmatory testing, represents the final stage in testing a drug for clinical approval. Such studies are typically rigorous, prospective, randomized, double blind, placebo-controlled trials of at least 6 months in duration and involve hundreds if not thousands of patients. Prespecified primary and secondary endpoints are defined in a hierarchal order, with consideration of the final indication and wording of the label if the drug is eventually approved.

Table 4. Factors that Might Account for Why Positive Results in the Laboratory do not Translate to Effective Therapies for Patients.

- Unanticipated side effects (clinical and laboratory)
- Animal models do not accurately reflect the human disease
- Selection of incorrect dose for clinical trial
- Wrong population studied
- Wrong clinical trial design
- Insensitive or incorrect clinical endpoint

New Drug Application

Typically, positive efficacy results in two separate Phase III studies are required for approval of a new molecule or intervention. Regulatory agencies such as the FDA also typically require an acceptable safety profile based on a database of at least 600 subjects who have been treated with the intervention for at least 6 months in placebo-controlled studies (US Department of Health and Human Services, Food and Drug Administration, CEDR, and CBER. Guideline for industry: The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of NonLife-Threatening Conditions. ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), March 1995), controlled data on 100–200 subjects who have received treatment for 1 year, and a total of about 1500 subjects who have been exposed to the drug for some period of time. Although this sounds like a large number of patients, particularly for an academic researcher, it is a relatively small number considering the number of persons who could be exposed to the agent if the drug is approved for marketing. The FDA also requires postmarketing surveillance to track side effects, as some are only appreciated after a very long-term exposure or after tens of thousands of patients have been exposed to them.

The regulatory requirements for approval of a new treatment, the ultimate endpoint of translational experimental therapeutics, involve a complex process with national peculiarities and quirks. The New Drug Application (NDA) process within the US can take many years and cost tens of millions of dollars. Meetings prior to submission of the NDA can facilitate the process by helping to identify FDA's concerns about the adequacy of the data with respect to demonstrating safety and efficacy. In situations with new classes of therapeutic agents or in circumstances of uncertainty, the FDA may seek the advice of an advisory committee (www.fda.gov/oc/advisory). There are approximately two dozen such advisory committees that support the various therapeutic areas within the different offices of the FDA (drug, biologic, and device areas). Ultimately, the FDA will negotiate directly with the sponsor of the NDA in determining whether a drug has suitable data to support its approval for use in medical practice, what the exact indication for the intervention will be, and how the label will be worded.

DOI:10.1002/MSJ

Why do Drugs that Work in the Laboratory Fail in Clinical Trials?

It is important for the reader to appreciate that the large majority of drugs that initially start on the "translational experimental therapeutics" pathway fail to complete the development process, and some fail to gain FDA approval, despite a full preclinical and clinical trial package having been obtained. Thus, the amortized cost of the average new drug coming to market in the United States at the present time is in the range of 1 billion dollars. Some of the reasons for this failure have been discussed in this review and include unanticipated clinical and laboratory side effects or lack of efficacy in preclinical or human studies, and technical problems with drug pharmacokinetics and manufacture. These problems, although discouraging, are to be expected. What is more disconcerting are the number of agents that are well tolerated and do not have side effects, but fail to provide efficacy in clinical trials despite compelling laboratory evidence suggesting that these agents should have been effective. A recent example is TCH-346, a propargylamine that was tested as a putative neuroprotective agent in PD and amyotrophic lateral sclerosis.[24] The drug had powerful and profound protective effects on many different types of motor neurons in a wide variety of preclinical models, but had no beneficial effects on any of the preselected primary or secondary outcome measures in clinical trials. It is interesting to speculate on the reasons why this kind of situation might occur (Table 4). Firstly, laboratory changes upon which a new treatment is based may represent secondary or epiphenomena and not directly relate to the cause of the disease. Thus, the treatment may be miscalculated from the outset. Secondly, the preclinical models in which new interventions are tested may not reflect the etiopathology of the disease process, and may, therefore, not be predictive of the effect of the agent in the human disease state. Tissue culture is very remote from the human patient, and it is not clear that any results obtained *in vitro* will directly bear on what will occur in the human disease. Further, many animal models are not precise replicas of the etiopathogenesis of the human illness that is being studied. Thus, positive, or for that matter negative, results in these models may have little or no predictive relevance as to whether or not a new intervention will prove helpful for human patients with the target disease. Thirdly, it may be essential to deliver drugs to target sites at more precise concentrations than we can currently attain if we are to see a comparable effect to that observed in an animal model. Translating the dose of a drug that provides positive results in animal models to an effective dose in humans is an imprecise art, and it is possible that studies testing drugs in thousands of patients and costing tens of millions of dollars may have had no chance of working in the first place because of the dose selected. This is a particular problem when testing a drug in a chronic disease when there is no progressive animal model in which to test the potential disease-modifying properties of the drug, and where there are no biologic markers of disease progression. Finally, clinical trial issues such as the patient population and trial design may limit the possibility of detecting the desired effect. Most importantly, the wrong clinical endpoint may have been chosen. It is important to have a clinical endpoint that accurately measures the effect of the agent on the disease process, and not an unrelated biomarker. Reduction in pain may not herald a fundamental improvement in the underlying arthritis or neuropathy. Reducing levels of homocysteine may not address the fundamental causative problem and may not reduce the risk of heart disease, stroke, or dementia observed in patients with high homocysteine levels. And treatment-induced change in an imaging biomarker of a disease process does not necessarily imply that the drug has an effect on the disease process itself. It is also important to select an endpoint that is not readily confounded, thereby impairing detection of the desired effect. For example, it may be difficult to differentiate small changes in an outcome measure of a disease state that result from trivial symptomatic effects of a new drug from important disease modifying effects.[25]

Conclusions

The concept of translational experimental therapeutics involves the establishment of an effective and safe therapeutic intervention for a disease state based on scientific advances made in the laboratory. This process includes the development of novel interventions targeted at a laboratory-defined pathophysiological mechanism, testing the intervention in laboratory models, and appropriate human experimentation (Table 1). Determining the scientific basis for a disease mechanism and establishing benefit and safety in relevant animal models are important initial steps in that process. Subsequent introduction of the intervention to humans with careful monitoring of safety and disease response are the next steps. Selection of the correct dose and utilization of clinical endpoints or outcome measures that accurately reflect the effect of the intervention on the proposed target disease are

DOI:10.1002/MSJ

critical to the drug development process, and remain important challenges. It is discouraging to consider that the scientific advances taking place in the laboratory today are outstripping our ability to translate them into effective therapies. Further insights into the cause of individual diseases, the development of more relevant and predictive animal models, better ways to determine the optimal dose for a given therapy, and more accurate ways to assess the impact of a drug on a disease state are urgently required, if the high expectations of translational science are to be realized soon.

It has also not failed to catch our attention that clinical researchers in the first half of the twentieth century had considerable success in developing new therapies for clinical disorders without the scientific resources available today. It should be noted that effective treatments for depression, epilepsy, psychosis, and anxiety were developed largely on the basis of clinical observations made by astute physicians, sometimes in individual patients, and it is interesting to speculate upon how many of these drugs, which have benefited so many millions of patients, would have been discovered if we relied exclusively on translational research and how many could have made it through today's demanding and expensive regulatory approval process.

References

1. Ioannidis JPA. Evolution and translation of research findings: from bench to where? *PLoS Clin Trials* 2006; 1(7): e36. DOI: 10.1371/journal.pctr.0010036.
2. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA* 2005; 294: 3003–3010.
3. Bilen J, Bonini NM. Drosophila as a model for human neurodegenerative disease. *Annu Rev Genet* 2005; 39: 153–171.
4. Artal-Sanz M, de Jong L, Tavernarakis N. Caenorhabditis elegans: a versatile platform for drug discovery. *Biotechnol J* 2006; 1: 1405–1418.
5. Bruijn LI, Houseweart MK, Kato S, et al. Aggregation and motor neuron toxicity of an ALS-linked SOD1 mutant independent from wild-type SOD1. *Science* 1998; 281: 1851–1854.
6. Games D, Adams D, Alessandrini R, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F ß–amyloid precursor protein. *Nature* 1995; 373: 523–527.
7. Mangiarini L, Sathasivam K, Seller M, et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell* 1996l; 87: 493–506.
8. Klivenyi P, Ferrante RJ, Matthews RT, et al. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. *Nat Med* 1999; 5: 347–350.
9. Groeneveld GJ, Veldink JH, van der Tweel I, et al. A randomized sequential trial of creatine in amyotrophic lateral sclerosis. *Ann Neurol* 2003; 53: 437–445.
10. Shefner JM, Cudkowicz ME, Schoenfeld D, et al. A clinical trial of creatine in ALS. *Neurology* 2004; 63: 1656–1661.
11. Melrose HL, Lincoln SJ, Tyndall GM, Farrer MJ. Parkinson's disease: a rethink of rodent models. *Exp Brain Res* 2006; 173: 196–204.
12. Gimenez-Llort L, Blazquez G, Canete T, et al. Modeling behavioral and neuronal symptoms of Alzheimer's disease in mice: a role for intraneuronal amyloid. *Neurosci Biobehav Rev* 2007; 31: 125–147.
13. Department of Health and Human Services, Food and Drug Administration. International conference on harmonisation: guidance on general considerations for clinical trials. *Fed Regist* 1997; 62: 66113–66119.
14. Hermann DM, Ertugrul K, Spudich A, et al. Role of drug efflux carriers in the healthy and diseased brain. *Ann Neurol* 2006; 60: 489–498.
15. Raucy JL, Allen SW. Recent advances in P450 research. *Pharmacogenomics J* 2001; 1: 178–186.
16. Lee MD, Ayanoglu E, Gong L. Drug-induced changes in P450 enzyme expression at the gene expression level: a new dimension to the analysis of drug-drug interactions. *Xenobiotica* 2006; 36(10–11): 1013–1080.
17. Hancox JC, Mitcheson JS. Combined hERG channel inhibition and disruption of trafficking in drug-induced long QT syndrome by fluoxetine: a case-study in cardiac safety pharmacology. *Br J Pharmacol* 2006; 149: 457–459.
18. Schneider V, Levesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal anti-inflammatory drugs with acute renal failure: a population-based, nested case-control analysis. *Am J Epidemiol* 2006; 164: 881–889.
19. Zerhouni E. Policy forum: the NIH roadmap. *Science* 2003; 302: , 63–64 72.
20. Zerhouni EA. US biomedical research: basic, translational, and clinical sciences. *JAMA* 2005; 294: 1352–1358.
21. Hurko O, Ryan JL. Translational research in central nervous system drug discovery. *NeuroRx®* 2005; 2: 671–682.
22. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. July 7, 2005; J: \GUIDANCE 5541fnlclnl.docl 1–27.
23. Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med* 2006; 355: 1018–1028.
24. Olanow CW, Schapira AHV, Lewitt PA, et al. TCH346 as a neuroprotective drug in Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol* 2006; 5: 1013–1020.
25. Schapira AHV, Olanow CW. Neuroprotection in Parkinson's disease: Myths, mysteries, and misconceptions. *JAMA* 2004; 291: 358–364.

DOI:10.1002/MSJ

Foundations, Promises and Uncertainties of Personalized Medicine

Erwin P. Bottinger

Charles Bronfman Institute for Personalized Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, New York

Abstract

Personalized medicine introduces the promise to use molecular markers that signal the risk of disease or its presence before clinical signs and symptoms appear. This information underlies a new healthcare strategy focused on prevention and early intervention, rather than reaction to advanced stages of disease. Such a strategy can delay disease onset or minimize symptom severity. The molecular foundations that enable personalized medicine include detection of variation in nucleotide sequence of genes and in characteristic patterns of gene expression, proteins and metabolites. Genetic and molecular patterns are correlated with disease manifestations, drug responses, treatment prognosis, or prediction of predisposition to future disease states. However, the uncertainties for personalized medicine are considerable, including economic, ethical, legal, and societal questions. Although much of its promise remains unproven to date, the foundations of personalized medicine appear solid and evidence is accumulating rapidly pointing to its growing importance in healthcare (Fig. 1). ***Mt Sinai J Med 74:15–21, 2007.*** © *2007 Mount Sinai School of Medicine*

Key Words: genomics, preventive medicine, pharmacogenomics, bioethics.

Address Correspondence to:

Erwin P. Bottinger
Charles Bronfman Institute for Personalized Medicine
Department of Medicine
Mount Sinai School of Medicine
One Gustave L. Levy Pl.
Box 1118
New York, NY 10029
Email: Erwin.bottinger@mssm.edu

Foundations for Personalized Medicine

Genetic Heterogeneity as Foundation for Personalized Medicine

Genetics became an increasingly important part of medical research and practice in the late 1950s. Initially, the field focused on diseases due to a single defective gene that could be traced through families in a way that followed Mendel's laws of inheritance, or disorders due to defects in the structure or number of chromosomes.[1] In contrast, most common human diseases and drug responses are polygenic, requiring the action of several gene variants. These traits or diseases are also called complex traits.[2] The concept of genetic linkage and its application to discovering genes associated with diseases and complex traits has been one of the major technical advances in modern molecular genetics.[2] Fundamental to this concept is the identification of sites of variation in the sequence of the genome. Although human DNA sequences are 99.9% identical to each other, the remaining 0.1% of variation is of great interest.[3]

Single Nucleotide Polymorphisms and Haplotypes

When a variation in DNA between individuals is found sufficiently frequently in normal populations, it is referred to as a polymorphism. Examples of polymorphisms include single nucleotide polymorphisms (SNPs), insertions and deletions of nucleotides, and repetitive sequences (microsatellites). SNPs may occur in linked groups called haplotypes, defined as a combination of alleles from closely linked loci found on a particular chromosome. Millions of known sites in the genome vary between different people and provide linkage markers for extensive studies of families or populations. Their ethnic distribution is a natural representation of the genetic evolution of humans.[4] Current data suggest that the median difference in allele frequency between major

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20005

© 2007 Mount Sinai School of Medicine

ethnic groups is between 15 and 20%. This means that very common alleles (those present in more than 20% of the population) tend to be shared, whereas rarer alleles may be specific to an ethnic subset of the population.[5] SNP analysis is being used to investigate the genetic basis of susceptibility of common diseases and variation in drug response and metabolism. Only SNP that fall in a protein-coding region of a gene, or within control regions of DNA that govern the gene's activity, are likely to make a difference to the gene product. Knowledge about the number and genomic location of polymorphisms has risen rapidly in the past 10 years. The total number of common SNPs in the human genome is now estimated at over 10 million (see Entrez SNP database (2005). National Center for Biotechnology Information. Available online at www.ncbi.nlm.gov/entrez/query.fcgi?db=snp).

Genetic data for haplotype analysis are available from the HapMap project.[6] The goal of the project is to develop a haplotype map of the human genome that will describe the common patterns of human DNA sequence variation, including haplotype frequencies among population samples from Nigeria, Japan, China and the USA. An important objective of haplotype mapping is to identify those SNPs that "tag" or identify SNP variation in haplotype blocks (tag SNPs).[7,8] This could reduce genotyping costs by severalfold and enable large-scale genotyping projects that would otherwise be too expensive. The number of tag SNPs needed will vary with the amount of linkage disequilibrium in a region, and the required statistical power for the study.[9] The optimal strategies for using sets of tag SNPs are currently under development and are the subject of much debate. In particular, the number of SNPs that will be required to determine the spectrum of common and rare variations that underlies individual disease risk or drug response.

At present new technologies for sequencing are being developed that combine the accuracy of current sequencing techniques with lower costs. Overall, these approaches should be able to improve today's sequencing methods by several orders of magnitude. Although this technology is improving there are still many difficulties to be overcome in matching phenotypes, disease susceptibility or variations in drug response, to SNP haplotypes.

Large scale association studies of SNPs or haplotypes and either disease risk or drug response are prone to both false-positive and false-negative results, which might arise by chance given the multiplicity of tests that are typically performed in gene association studies. To overcome these problems, studies will need to be large, involving thousands of people, particularly, if associations are to be examined for substrata of the population, for example by age, gender, ethnicity, disease group or lifestyle characteristics. Problems can also arise if the population sample includes people from different ethnic groups with different population structures.[10] Replication studies will be required, either in a different study, population or substrata.

Promises of Personalized Medicine

Advances in Genomic Testing for Clinical Practice

Genomic tests may be conducted on the person (to test for inherited variation) or on the disease tissue (currently confined to oncology). The test conducted would usually be an examination of genomic sequence looking for specific variants, but could include expression analysis–a quantitative or qualitative determination of the messenger RNA transcribed in a tissue or organs. Genomic tests may also include the examination of protein products, or functional tests, also designed to reveal genetic differences in the target individual or tissue (Fig. 2). With the range of these tests, several goals for clinical genomic testing cover the spectrum of personalized medicine applications (Table 1). The first goal is the subdivision or molecular segmentation of common diseases into different molecular subtypes, which may be more or less susceptible to specific treatments. Secondly, genomic testing should support the evolution of more logical approaches to drug dosage, efficacy and the prevention of adverse reactions by analyzing the genetic basis for differences in the pharmacodynamic or pharmacokinetic properties of drugs. Finally, by identifying determinants of genetic susceptibility to various common diseases, genomic

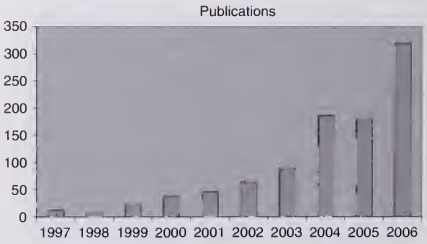


Fig 1. PubMed search with keywords "personalized medicine" by calendar year.

DOI:10.1002/MSJ

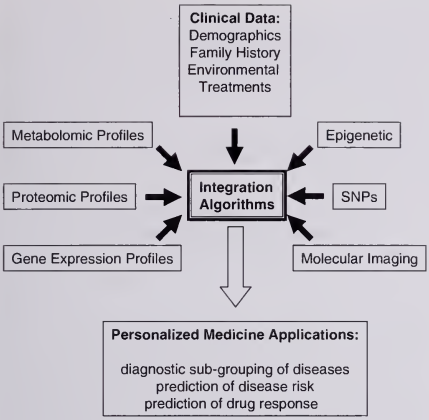


Fig 2. Integration of molecular, clinical, and other data to enable personalized diagnostics and personalized risk predictions.

testing should offer new targets that may be evaluated for pharmacological intervention. These goals for clinical genomic testing are discussed further in the following sections.

The most progress in refining molecular heterogeneity of common diseases has been achieved in cancer research. Two genetic tests now on the market can identify disease susceptibility and guide preventive care. One is a test for BRCA1 and BRCA2 genetic variants that indicates hereditary propensity for breast and ovarian cancer.[11] Women with BRCA1 or BRCA2 genetic risk factors have a 36 to 85% lifetime chance of developing breast cancer, compared with a 13% chance among the general female population. For ovarian cancer, women with certain BRCA1 or BRCA2 gene variants have a 16 to 60% chance of contracting the disease, compared with a 1.7% chance among the general population. Use of the BRCA1 and BRCA2 genetic test can be used to guide preventive measures, such as increased frequency of mammography, prophylactic surgery, and chemoprevention. The second currently available genetic test is the p16 test for melanoma.[12] P16 accounts for up to 40% of hereditary cases of melanoma and has also been linked to pancreatic cancer. For those who test positive, several prevention options are available, including early detection, preventive surgery on suspicious lesions, and reduced sun exposure. The treatment of early stage breast cancer in women may be transformed by several assays in development that scan a panel of genes correlated with risk of disease recurrence and response to therapy.[13] One such assay now being used in clinical settings is Onco*type* DX, which analyzes the expression of 21 genes.[14] The information provided by this test supports both treatment and monitoring decisions based on the foreknowledge of disease progression, time to event, and likelihood of treatment benefit.[15]

Pharmacogenomics

Tests to Predict Drug Efficacy

Studies have linked differences in drug responses to differences in genes that code for the production of drug-metabolizing enzymes, drug transporters, or drug targets.[16–18] Detection of these genetic differences provides the opportunity to use genetic or other forms of molecular screening to select optimal therapy the first time and avoid a trial-and-error approach to prescribing. For example, about 30% of breast cancers are characterized by overexpression of a cell surface protein called human epidermal growth factor receptor 2 (HER2).[19] In normal quantities, HER2 promotes normal cell growth. But when a genetic mutation causes HER2 to be overexpressed on the cell surface, certain breast cells are prompted to multiply uncontrollably and invade surrounding tissue.[19] Women with HER2-positive breast cancer do not respond well to standard therapies. Development of an antibody drug–Herceptin(trastuzumab)–that specifically inhibits the HER2 receptor has greatly improved the survival rate of women with this deadly form of cancer.[20] Molecular diagnostic tests have been developed that measure either HER2 protein levels or gene copy numbers to identify patients who will benefit from receiving Herceptin.

Gleevec (imatinib), another successful example of personalized medicine, is used in the treatment of chronic myelogenous leukemia (CML) and malignant gastrointestinal stromal tumors. CML is caused by a chromosomal rearrangement that creates a fusion between two normal proteins, producing one abnormal protein called Bcr-Abl that promotes a rapid increase in the number of white blood cells. Gleevec binds specifically to Bcr-Abl and inhibits its action. Appropriate prescription of the drug can be confirmed by a diagnostic test that detects the presence of the *BCR-ABL* gene. Studies show vastly improved response rates and lower toxicity for CML patients receiving Gleevec compared with patients receiving standard chemotherapy.[21] Recently, a genetic test to monitor the emergence of Gleevec resistance has been introduced. Gleevec resistance occurs in about 4 to 5% of CML cases (Genzyme 2006). This new test could provide an additional tool for personalization of treatment.

DOI:10.1002/MSJ

Table 1. Proposed benefits of personalized medicine[a].

- Detect disease at an earlier stage, when it is easier to treat effectively
- Enable the selection of optimal therapy and reduce trial-and-error prescribing
- Reduce adverse drug reactions
- Increase patient compliance with therapy
- Improve the selection of targets for drug discovery
- Reduce the time, cost, and failure rate of clinical trials
- Revive drugs that failed clinical trials or were withdrawn from the market
- Avoid withdrawal of marketed drugs
- Shift the emphasis in medicine from reaction to prevention
- Reduce the overall cost of healthcare

[a]Adapted from *The Case for Personalized Medicine* available at http://www.personalizedmedicinecoalition.org/communications/TheCasefor-PersonalizedMedicine_11_13.pdf

Tests to Guide Dosing and Avoid Adverse Drug Reactions

Studies estimate that over 2 million serious adverse drug reactions (ADRs) occur annually in the United States, causing as many as 137,000 deaths. Some of these deaths could be prevented by testing individuals for genetic variations indicating their susceptibility to toxic reactions. Many adverse drug reactions are caused by variations in genes coding for enzymes. Enzymes are complex proteins that catalyze chemical reactions in the body, such as the metabolism of nutrients or drugs. About half of all drugs are metabolized by the cytochrome P450 family of enzymes present in the liver and gastrointestinal tract (BCBS 2004). There are over 30 different forms of these enzymes, each coded for by a different gene. Variations in these genes can lead to decreased or increased metabolism of certain drugs. As a result, some individuals may have trouble inactivating a drug and eliminating it from their body, while others eliminate the drug before it has a chance to work. For drugs that are metabolized too slowly, there is an increased risk for patients to be "overdosed" when given a typical dose, possibly resulting in serious toxicity. The FDA has approved the Amplichip cytochrome P450 test, which can detect variations in two important *cytochrome P450* genes.[22] The information provided by Amplichip and similar tests will help physicians make better decisions about drug treatments and dosages. The UGT1A1 assay was also approved by the FDA to predict patients' safety-related responses to irinotecan used in the treatment of colon cancer. The test allows physicians to adjust the irinotecan dosage for the approximately 10% of patients who metabolize the active form of the drug too slowly. Administration of the drug warfarin, used to prevent blood clots, is complicated by genetic variations in a drug metabolizing enzyme (CYP2C9) and a vitamin K metabolizing enzyme (VKORC1).[16] Dosing is typically adjusted for the individual patient through multiple rounds of trial and error, during which the patient may be at risk of excessive bleeding or further blood clots. The need to get warfarin dosing right the first time to avoid adverse effects led an FDA advisory committee to recommend genotyping for all patients receiving warfarin. An actual revision of the drug label awaits the results of a definitive clinical study. Thiopurine methyltransferase (TPMT) is another enzyme that has been studied from a personalized medicine perspective. TPMT is responsible for inactivating purine drugs used for treating acute lymphoblastic leukemia (ALL) and other diseases.[23,24] TPMT gene variations can cause variations in enzymatic activity and thus drug metabolism. One in 300 patients has both copies of their TPMT genes coding for an inactive form of the enzyme, a condition known as TPMT deficiency. In these patients, the normal dose of purine drugs results in an accumulation of active compound, which may cause a potentially fatal bone marrow reaction that results in an abnormal lowering of the white blood cell count. After a few cases of fatal toxicity in TPMT-deficient ALL children treated with a purine drug, physicians started screening for variations in the TPMT gene before administering the drug. When a TPMT deficiency is detected, the dose is lowered to 10 to 15% of the standard dose. This adjustment ensures that systemic levels of the drug are comparable to those found in patients with normal TPMT who have been given a standard dose.

Improving Clinical Trials

Personalized medicine provides a new economic model of drug development that benefits both pharmaceutical companies and patients. For example, clinical trials of Herceptin and Gleevec leading to initial regulatory approval were conducted in a relatively small number of patients qualified by specific biomarkers. The use of these biomarkers permitted

DOI:10.1002/MSJ

clearer results in clinical trials and faster, less expensive paths to FDA approval. Encouraged by these success stories, several major pharmaceutical companies are targeting diseases with a smaller defined patient population in order to reduce the initial cost and duration of clinical trials, and then later expanding the drugs' indications to other related diseases.[25]

Uncertainties and Challenges for Personalized Medicine

Cost-effectiveness

The aim of any evaluation of health economics is to determine how healthcare resources can be used most prudently. Using the tools of health economics, the analysis of cost-effectiveness in pharmacogenomics and personalized medicine can be used to examine the clinical and economic impact of such interventions. In pharmacogenomics, many of the new technologies will be competing with existing methods of diagnosis and treatment. As such, they will need to undergo rigorous evaluation in large-scale trials. Although the introduction of pharmacogenomic testing has the potential to reduce costs through improved interventions, greater efficacy, less inappropriate prescribing and fewer ADRs, it is not clear whether or not the tests will increase or decrease overall health costs. This is because of the costs of developing, evaluating and implementing pharmacogenetic testing; associated costs of training and clinical time needed to administer and interpret the tests effectively; and auditing their use in a health service setting. While the assessment of cost-effectiveness is relatively well developed in the healthcare system, its application to pharmacogenomics and personalized medicine is far less developed. In general, personalized medicine therapies and diagnostic tests have not yet prompted widespread review and cost-effectiveness analysis, but a number of studies that have been conducted provide some interesting insights, as well as preliminary validation of the economic benefits of personalized medicine in the delivery of healthcare.[26]

Reimbursement

Adequate and timely coverage and reimbursement by insurers are also critically important to the adoption of personalized medicine therapies. In many cases, reimbursement follows regulatory approval. For example, the joint FDA approval of both Herceptin and a diagnostic test for determining which breast cancer patients would benefit from Herceptin paved the way for reimbursement of both products by most third party payers. Medicare reimbursement policy for diagnostic tests is usually based on confirming traditional diagnosis of existing signs and symptoms. Such an approach can discourage adoption of molecular tests, which may be more predictive in nature. Reimbursement policies will have to be realigned to support a more preventive, proactive approach to medicine. Medicare coverage of Herceptin/Herceptest and the gene expression profile Onco*type* DX portends an increasing awareness among payers of the value of personalized medicine. Keeping formulary policy up to date with personalized medicine will also be important to adoption by physicians and patients.

Ethical and Societal Considerations

Ethical considerations surrounding the translation of personalized medicine research into practice are focused on the principles of consent, privacy and confidentiality. A number of key tenets have emerged. For example, the use of genomic information collected in research relies on the voluntary nature of the consent but concerns arise about the privacy of the information that is obtained and stored. Genuine voluntary consent may be difficult to obtain in clinical trials or in clinical practice when, for example, routine genotyping from DNA is part of the trial or clinical process, which may be difficult to refuse. Privacy and confidentiality measures must be in place to protect participants in research. However, concerns about the anonymity of samples and its compatibility with fulfilling the objectives of the research remain to be addressed. Genomic stratification of disease may prove to be an economic disincentive for those developing new medicines. This may require the adaptation of existing orphan medicine legislation. Genomics and ethnic groups requires further scrutiny as there is a danger that ethnicity, rather than genetic profiling, may be used in the allocation of pharmacogenetic tests and medicines. Health professionals will require education and training to communicate genomic information, and the associated risks to patients. Finally, privacy and confidentiality of genomic information could have implications for family members. This could lead to circumstances in which the obligation of health professionals to their individual patients comes into conflict with their obligations to others, which may lead to encouraging patients to share genomic information with family members.

DOI:10.1002/MSJ

Genetic Information Nondiscrimination

Currently, federal and state laws offer only a patchwork of protection against the misuse of genetic information. To fulfill the promise of personalized medicine, basic genetic nondiscrimination legal protections need to be established in order to enable and encourage individuals to participate in research, and take full advantage of genetic screening, counseling, testing, and new therapies. Although the public is generally supportive and anticipatory of personalized medicine, the fear of genetic discrimination in employment and health insurance is a significant obstacle to full participation. Proposed legislation, such as the Genetic Information Nondiscrimination Act of 2005, suggests that most of the gaps in privacy protection can be covered. One survey indicated that about half of the public (48%) is interested in using genetic information to understand and optimize their health. The degree to which physicians utilize personalized medicine will be limited by their knowledge of the subject and their awareness of available tests and treatments. Most medical education institutions have not incorporated personalized medicine into their curricula. Educational programs will be necessary to prepare a healthcare workforce capable of administering personalized medicine.

Transformation of Academic Medical Centers to Enable Personalized Medicine

Electronic Clinical Data and Sample Repositories

Genomic testing will generate vast quantities of data, much of it unintelligible to the healthcare provider. Genetic testing differs from most other laboratory tests as it potentially gives a result that can last a lifetime, which will need to be recorded and stored in an electronic medical record (EMR). Interpretation and use of genomic testing will require informatics solutions combine morbidity, information on medications, age, gender and lifestyle such as occupation and smoking, to provide a risk analysis. It is likely that a variety of SNPs will be involved, so dedicated informatics solutions may be needed for the clinician to aid interpretation of the results of tests. The results, with interpretation, will need to be available to all clinicians, including nurses and pharmacists (community and hospital) who are prescribing, so the ability to access rapidly up-to-date data in primary-, secondary- and tertiary-care settings will be required. The availability of electronic data about patients in the health service, linking prescription data for individual patients with clinical outcomes, will enable new uses to be made of the data for research and audit. Widespread adoption of electronic medical records will play an important role in preparing our health system for personalized medicine, providing rapid access to both clinical information and molecular test results so patients and physicians can make optimal treatment decisions. EMRs will also accelerate the treatment discovery cycle by providing researchers with access to large databases of (anonymous) patient data. Relating findings from the electronic medical record back to genotypic data will require access to biological samples from individual patients, or stored genetic data, and the identification of a representative control group within the database.

Education of Healthcare Workforce

Because there seems little doubt that genomics will play an increasingly important role in clinical practice, doctors, nurses, and pharmacists of the future will require a much stronger basic training in the fundamentals of human genetics than they have received hitherto. Education in genetics at undergraduate, postgraduate and continuing medical education levels has trailed behind the enormous scientific and technical advances in this field. Knowledge about simple inherited conditions, such as cystic fibrosis or Duchenne muscular dystrophy, has improved diagnosis for patients and their families and provided them with alternative options for reproduction. Clinical genetics promotes nondirective consulting and addresses consent and confidentiality for patients. One area of urgent need is for a renewed focus on training in clinical pharmacology. During the 1940s and 1950s many drugs were discovered that are still the basis for much of our current prescribing. Because of the need to study their effects in humans, the discipline of clinical pharmacology emerged, both in academia and industry.

Conclusions

Currently, the evidence establishing a clear-cut case for personalized medicine remains largely anecdotal rather than statistical, but that is to be expected for such a nascent field. In oncology, there are many proofs of principle for personalized medicine, and many more are emerging. Multiple examples have demonstrated the utility of personalized medicine in selecting optimal therapy, rescuing drugs from failed clinical trials, and shifting emphasis from disease treatment to disease prevention. Furthermore, little

DOI:10.1002/MSJ

hard evidence is available on the impact of a personalized medicine approach on pharmaceutical industry productivity or healthcare economics.

Whether personalized medicine will transform clinical care is uncertain. However, at least in some cases, a personalized medicine approach to treatment has led to cost savings in the administration of healthcare, demonstrated itself to be a viable business strategy for product development, and most importantly, proven its benefit to patients. It is therefore reasonable to expect that many more successful examples of personalized medicine will be seen in the near future.

References

1. Meyer UA. Pharmacogenetics–five decades of therapeutic lessons from genetic diversity. *Nat Rev Genet* 2004; 5(9): 669–676.
2. Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet* 1995; 11(3): 241–247.
3. Ziv E, Burchard EG. Human population structure and genetic association studies. *Pharmacogenomics* 2003; 4(4): 431–441.
4. The International HapMap Cousortium The International HapMap Project. *Nature* 2003; 426(6968): 789–796.
5. Burchard EG, Ziv E, Coyle N, et al. The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med* 2003; 348(12): 1170–1175.
6. Thorisson GA, Smith AV, Krishnan L, Stein LD. The International HapMap Project Web site. *Genome Res* 2005; 15(11): 1592–1593.
7. Zeggini E, Rayner W, Morris AP, et al. An evaluation of HapMap sample size and tagging SNP performance in large-scale empirical and simulated data sets. *Nat Genet* 2005; 37(12): 1320–1322.
8. Willer CJ, Scott LJ, Bonnycastle LL, et al. Tag SNP selection for Finnish individuals based on the CEPH Utah HapMap database. *Genet Epidemiol* 2006; 30(2): 180–190.
9. Hinds DA, Stuve LL, Nilsen GB, et al. Whole-genome patterns of common DNA variation in three human populations. *Science* 2005; 307(5712): 1072–1079.
10. Marchini J, Cardon LR, Phillips MS, Donnelly P. The effects of human population structure on large genetic association studies. *Nat Genet* 2004; 36(5): 512–517.
11. Nelson HD, Huffman LH, Fu R, Harris EL. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2005; 143(5): 362–379.
12. Begg CB, Orlow I, Hummer AJ, et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *J Natl Cancer Inst* 2005; 97(20): 1507–1515.
13. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; 351(27): 2817–2826.
14. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006; 24(23): 3726–3734.
15. Hornberger J, Cosler LE, Lyman GH. Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. *Am J Manag Care* 2005; 11(5): 313–324.
16. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 2005; 352(22): 2285–2293.
17. Terra SG, Hamilton KK, Pauly DF, et al. Beta1-adrenergic receptor polymorphisms and left ventricular remodeling changes in response to beta-blocker therapy. *Pharmacogenet Genomics* 2005; 15(4): 227–234.
18. Terra SG, Pauly DF, Lee CR, et al. beta-Adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. *Clin Pharmacol Ther* 2005; 77(3): 127–137.
19. Menard S, Pupa SM, Campiglio M, Tagliabue E. Biologic and therapeutic role of HER2 in cancer. *Oncogene* 2003; 22(42): 6570–6578.
20. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; 353(16): 1659–1672.
21. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; 344(14): 1031–1037.
22. Jain KK. Applications of AmpliChip CYP450. *Mol Diagn* 2005; 9(3): 119–127.
23. Weinshilboum R. Inheritance and drug response. *N Engl J Med* 2003; 348(6): 529–537.
24. Wang L, Weinshilboum R. Thiopurine S-methyltransferase pharmacogenetics: insights, challenges and future directions. *Oncogene* 2006; 25(11): 1629–1638.
25. Penny MA, McHale D. Pharmacogenomics and the drug discovery pipeline: when should it be implemented? *Am J Pharmacogenomics* 2005; 5(1): 53–62.
26. Phillips KA, Van Bebber SL. Measuring the value of pharmacogenomics. *Nat Rev Drug Discov* 2005; 4(6): 500–509.

DOI:10.1002/MSJ

The Role of the Pathologist in Translational and Personalized Medicine

Daniel P. Perl, MD

Department of Pathology, Mount Sinai School of Medicine, New York, New York

Abstract

Over the years, pathologists have served to make morphologic diagnoses for clinicians when provided with a biopsy or surgically resected tissue specimen. Traditionally, pathologists have used a series of morphologic techniques and relied on the microscopic appearance of resected tissues to determine a pathologic diagnosis and, with respect to neoplastic lesions, provide predictions of the potential growth pattern that might be anticipated. With the introduction of the techniques of molecular biology in medicine, the role of the pathologist has changed as have the tools available for characterizing pathologic specimens. With the pathologist's unique perspective on disease processes and access to tissue specimens from the operating room, he has become a key player in the area of translational and personalized medicine and the development of new approaches to diagnosis and translational research. ***Mt Sinai J Med 74:22–26, 2007.*** © *2007 Mount Sinai School of Medicine*

Key Words: pathology, translational, transgenic, tissue bank.

Introduction

The pathologist has traditionally been thought of as a physician who wears an eosin-stained lab coat and performs autopsies somewhere in the hospital basement or provides anatomic diagnoses on myriads of surgical specimens and biopsies removed from living patients. In many settings, this stereotypic description has some validity; however, in the emerging era of translational and personalized medicine the role played by the pathologist has begun to change and has become considerably broader. Pathology, as the scientific study of the manner and means by which disease alters the form and function of normal tissues, has traditionally been a major contributor to establishing diagnoses and understanding the fundamental mechanisms which underlie disease processes. With the increasing use of the powerful new tools of radiologic imaging, genetics, and molecular biology, one might have assumed that the role of the pathologist would shrink in importance. As I will argue, the situation is quite the contrary and the need for the services and insights of the clinical and research pathologist has never been greater. This paper will provide examples of how advances in translational and personalized medicine offer opportunities for enhanced pathologic diagnosis for patients and research study of animal models of disease.

Address Correspondence to:

Daniel P. Perl
Department of Pathology
Mount Sinai School of Medicine
New York, NY 10029
Email: daniel.perl@mssm.edu

Evaluation of Biopsy Specimens to Provide Individualized Prognostic Information

For over 100 years the diagnostic pathologist has been primarily responsible for performing morphologic evaluations on tissue specimens received from the surgical theater or the autopsy room. In the pathology laboratory, these studies primarily rely on gross inspection and light microscopic evaluation of tissues assisted by hematoxylin and eosin and other dyes that help to define tissue anatomy. In the second half of the 20th century this approach became significantly augmented by the additional information that could be provided by more specialized techniques. Immunohistochemistry permitted identification of a wide variety of normal cellular markers and more specific pathologic markers of disease processes. In many instances this has allowed the pathologist to visualize aspects of disease states that were never before recognized. The introduction

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20007

© 2007 Mount Sinai School of Medicine

of electron microscopy similarly permitted identification of pathologic alterations in subcellular organelles that were below the level of resolution of the light microscope. These approaches have aided in the classification of a wide range of diseases, particularly neoplastic lesions. In addition, they have provided insights into the nature of the cells participating in the pathologic process and helped to clarify underlying disease mechanisms. Using this type of information, plus an enormous amount of empiric morphologic observations, pathologists have been able to further refine the means by which diseases are defined, identified and classified. Accordingly, we are now able to characterize neoplastic lesions as being either benign, premalignant, or malignant and to predict with a reasonable degree of accuracy, important characteristics, such as their growth rate, tendency to recur, and risk of metastasis. By and large, this approach has served us well and remains the mainstay of the current practice of diagnostic pathology.

However, in recent years, the situation has begun to change as basic translational research and the molecular characterization of specific disease conditions has provided a new and powerful vision into the nature of a variety of lesions. This new approach promises to enable the pathologist to provide to the treating clinician more comprehensive information on the nature of a lesion, and to allow more accurate predictions of its growth characteristics and likely response to different modes of therapy. In addition, molecular approaches have also allowed for the identification of a genetic profile that is associated with increased risks of developing specific diseases. In essence, such molecular characterization involves the evaluation of two separate and sometimes interrelated substrates, namely, the host individual and the specific nature of the pathologic lesion encountered in that patient. For example, it has become increasingly appreciated that a number of genetic conditions carry with them an increased risk for the subsequent development of various forms of cancer. The identification of the presence of such an underlying condition can therefore, provide important information for treating clinicians and signal the need for targeted cancer surveillance in the patient as well as in other family members. For example, individuals with mutations of the tumor suppressor gene PTEN suffer from Cowden's syndrome, which is characterized by the development of multiple hamartomatous lesions in tissues derived from all three germ cell layers. However, it is also now recognized that such patients are also at greatly increased risk for developing a variety of malignancies, including breast (25–50% lifetime risk) and thyroid (10% lifetime risk) cancers.[1]

Molecular characterization of neoplastic tissues, as opposed to that of the host, also has the potential to provide important information on such a lesion's potential to grow, recur after resection, respond to specific forms of chemotherapy, etc. In recent years, the molecular characterization of neoplastic lesions has become well established and is now standard practice in the field of hematologic oncology. Here the morphologic evaluation of the bone marrow aspirate represents the starting point in the diagnostic workup of a patient with leukemia. The classic pathology report with its morphologic assessment is now routinely accompanied by the use of fluorescence-activated cell sorting techniques to identify specific cell types as well as more detailed evaluation of the genetic characteristics of the malignant cells through the use of cytogenetic and molecular phenotyping.[2,3] All of this information is utilized to give a more complete and meaningful characterization of the nature of the neoplastic process and serves to provide a more accurate prediction of a malignant cell's potential to respond to specific forms of therapy.

Increasingly, the treating clinician strives to achieve a mode of therapy that has been individualized to the specific molecular phenotype of the lesion present in a specific patient, viewed in the context of the genetic make-up of that individual. This concept is referred to as personalized medicine and represents an approach in which research findings derived from translational approaches can be applied to individual patients. In theory, this approach allows for treatments to be tailored to the individual patient and his disease in an attempt to obtain maximal effectiveness. Additional approaches allow one to evaluate genetically based alterations of an individual patient's ability to metabolize specific drug therapies (pharmacogenetics). This overall approach offers great promise for the future, but currently remains largely theoretical, with only a very few instances (hematologic oncology, being one) in which this goal is beginning to be achieved.

A further example of the modern approach to pathologic diagnosis of a specific neoplastic lesion has occurred in the area of neuropathology, namely in the diagnostic characterization of oligodendroglial tumors (oligodendrogliomas). Oligodendrogliomas are a relatively uncommon form of primary glioma, comprising about 10% of all central nervous system gliomas. Gliomas as a group have a poor prognosis and are ultimately fatal. Over the years, it had been noted that of all the different forms of glioma, oligodendrogliomas have the highest rate of responsiveness to radiation and/or chemotherapeutic treatment (about 70% of

DOI:10.1002/MSJ

oligodendriomas show some response to therapy). Until recently, based on purely morphologic criteria, oligodendrogliomas were characterized as being anaplastic or nonanaplastic, with the implication that the former category had a more rapid growth pattern and thus a worse prognosis with more rapid progression of symptoms and death. This approach, employing purely morphologic criteria, appeared to work reasonably well. Under the banner of the World Health Organization (WHO)-sponsored grading system[4] nonanaplastic oligodendrogliomas are classified as WHO grade 2 while anaplastic oligodendroliomas are classified as WHO grade 3. This approach has been widely accepted and adopted by diagnostic neuropathologists.

However, the approach to oligodendrogliomas changed when the tumors began to be examined and characterized based on their underlying molecular characteristics.[5,6] Genetic analysis reveals that approximately 50% of oligodendrogliomas in adults are associated with deletions located at chromosomes 1p and/or 19q. It was further observed that deletions of both the 1p and 19q sites were associated with a poor response to chemotherapy and a significantly worse 5-year survival rate when compared to cases with only one of these deletions. One recent study showed that patients that lacked the 1p and 19q deletions had a substantially longer median survival time than those with these genetic markers (7.0 versus 2.8 years, respectively).[7]

While predicting oligodendroglioma chemotherapy response is hardly an everyday issue in clinical oncology, this represents an example where the molecular characterization of a patient's tumor can provide meaningful information that can more effectively guide treatment and predict outcome than routine histopathology. Indeed, some have argued that this information provides a more accurate outcome measure than the standard classic morphologic grading provided by experienced diagnostic neuropathologists.[8] In this situation, clearly both are needed, but here we have an example where proper clinical care will require that these extra steps be taken. It is highly likely that additional examples of the advantages of such molecular approaches will soon follow for other tumors of the nervous system as well as cancerous lesions encountered elsewhere in the body. Indeed, a very recent study reported a signature involving five genes which was associated with increased time of relapse-free survival among patients with non-small-cell lung cancer.[9]

Evaluation of Transgenic Animal Models of Disease

The ability to manipulate the genetic makeup of small animals through the use of transgenic approaches has radically enhanced our capacity to investigate human disease and to provide valuable animal models of a wide variety of conditions. As described by Kieburtz and Olanow in this issue of the Journal, transgenic animals that carry mutations associated with a variety of human diseases are now being widely used to study disease mechanisms, identify new targets for the development of new drugs, and to test putative disease modifying therapies. The animal species that has been most widely used to date is the mouse, but attempts are now being made to extend this to other species such as nematodes,[10] drosophila[11] and rats.[12]

In the production of transgenic animals, the pathologist is often called upon to perform morphologic evaluations to determine if structural lesions are present in genetically altered animals and, if so, how well they mimic the human disease that is being modeled. Transgenic animals frequently model only certain aspects of the human disease they are meant to represent, while other aspects of the disease are lacking. For example, Alzheimer's disease pathology is characterized by amyloid plaques, neurofibrillary tangles, and neuritic changes. For many years, transgenic mice were created that were touted as representing valid models of human Alzheimer's disease[13] because they expressed amyloid plaques, yet the neurofibrillary tangles, neuritic changes and other important pathologic features of the disease were missing in these models. Such transgenic animals may have considerable research value but it is important that these deficiencies in the model be recognized and considered in interpreting results. Pathologists are uniquely trained to be able to evaluate such models and recognize these distinctions. In some transgenic animals, the corresponding lesions produced in the transgenic mouse model match well with the human disorder, however, this is not always the case. Surprisingly, many attempts at generating transgenic animals have yielded either subtle or no identifiable morphologic abnormalities despite the fact that the transgenic animal carries the same gene mutation that induces the illness in humans. In other situations, the organ system or specific anatomical region that is involved in the human disease remains normal while other structures are identified as abnormal in the transgenic animal. There appears to be no way of predicting which outcome will be obtained. Either way, the mutant animal that is produced may still yield valuable information on gene/environment

DOI:10.1002/MSJ

interactions and how the mutant gene induces pathology of any type. In all cases, the transgenic animals must be carefully evaluated morphologically and compared to wild-type animals. Here, tissue examination by a knowledgeable pathologist is essential and can be very helpful in interpreting the utility of the model.

It should be appreciated that most pathologists trained in identifying human disease have little experience with mouse anatomy, particularly if one is looking at embryonic or neonatal specimens. On the other hand, most morphologists with expertise in mouse anatomy have little knowledge or understanding of the nature of the lesions present in association with human disease and the methods needed to display them to best advantage. A team approach is best here with the human pathologist providing insights into how well the transgenic mouse model mimics the disease, as it is seen in man.

Tissue Banking for Molecular Characterization

With the advent of genetic screening, gene microarray and proteomic technology, there has been an increasing trend for clinical and translational researchers to partner with anatomic pathologists to establish human tissue specimen banks to support such research.[14,15] Here, it is hoped that broadbased surveys of changes in DNA, RNA and protein expression in the tissues of patients with a variety of specific disease states will provide an important resource for studying disease etiology, pathogenic mechanisms, and the effects of drugs or interventions on a wide variety of outcome measures. The gene array microchip approach can provide a huge amount of data about a wide range of normal and pathologic cellular functions. Although at present this approach amounts to the ultimate "fishing expedition", the broad sweep of cellular functions and signaling pathways that can be assessed by such an approach promises to ultimately yield extremely valuable clinical information to both the basic researcher and the clinician. In addition, the capability of screening protein expression in the cell through proteomic methods, a technology which increases by orders of magnitude the amount of information that can be obtained, provides further avenues for similar investigation. The data sets that are generated by this approach are simply enormous and major investments and collaboration in the field of bioinformatics will be required to sort out the wheat from the chaff. Nonetheless, these approaches offer the basic scientist, clinician, and pathologist an opportunity to uncover specific cellular functions and signals that underlie or are associated with a myriad of disease processes, to predict the course and outcome of established diseases as well as identify individuals in the earliest stages of disorders, long before traditional clinical manifestations could be appreciated.

In order to carry out such studies one first needs access to large numbers of well-characterized, properly prepared and stored tissue samples with a minimum of autolytic degradation. This has stimulated pathologists to become involved in a growing movement to establish tissue banks by collecting and storing portions of the thousands of surgically derived tissue samples they receive in their laboratories for diagnostic evaluation as well as examples of normal tissues. The pathologist must play a key role in this process since he/she has immediate access to these tissues and controls (or at least should control) their proper handling and utilization. Additional banking opportunities may be derived from blood and other clinical samples and this has added to resources available. The pathologist, experienced in both anatomical and clinical laboratory operations, is unique in having the expertise and facilities needed to deal with the enormous number of samples that will be required for such an effort.

Of course it is essential that prior to their being prepared for banking, the specimens receive proper sampling for the diagnostic workup by the pathologist. The removal of portions of a tissue sample that are critical for this clinically essential process cannot be tolerated. For example, a specimen for cancer resection in which the margins cannot be properly checked for the adequacy of its removal because these portions have been accessioned for tissue banking is an unacceptable practice. It is important to recognize that tissue specimens that are banked for use in future research of this type are frequently not homogeneous and may have foci of necrosis, inflammation, cancer, etc. that are microscopic in size but may influence the results of future gene array and proteinomic studies. Based on the dramatic magnification of molecular approaches, such foci may either be missing or included in the specimen being analyzed and thus provide misleading data. The pathologist is the one individual who best understands these issues and can provide insights into how to interpret data obtained from specimens with such heterogeneous constituents.

The movement towards banking of normal and surgery-derived specimens has raised important

DOI:10.1002/MSJ

issues for consideration. It is essential that proper consent from the patient for the banking process includes allowing continued use of these tissues for research purposes. Who owns the banked tissues and has the rights of discovery on these specimens has recently emerged as a rather contentious issue.[16] Access to such banked tissue specimens by for-profit companies and who holds the rights to develop commercial products based on banked tissue-related studies have also raised concerns. What is to be done with clinical information associated with the specimen and what measures have been taken for providing anonymity also has to be established. What is to be done with the information derived from tissue samples obtained from clinically normal individuals that contain insights regarding the likelihood that they will develop cancer or dementia? These issues will have to be addressed, and most major academic medical centers are now actively engaged in addressing scientific, logistic and ethical issues involved in properly establishing tissue bank repositories to support work of this type.

Summary

Translational research is, by its very nature, cooperative research in which basic scientists partner with clinician scientists to bring new advances directly to the bedside. In such a cooperative arrangement, the pathologist stands between these two groups of scientists. Trained to recognize and understand how disease processes induce structural, biochemical, and functional alternations in tissues and organs, the pathologist provides an enormously powerful perspective to those looking to apply basic science findings directly to patients. Further, the pathologist's access to tissue specimens removed at surgery or at autopsy, provides a means by which DNA, RNA and protein expression may be characterized in disease states, especially cancer. As we now begin to move beyond the concepts of cellular pathology introduced by Rudolf Virchow in the latter part of the 19th century, it is clear that the pathologist will play a unique and increasingly critical role in furthering advances in translational and personalized medicine.

References

1. Pilarski R, Eng C. Will the real Cowden syndrome please stand up (again)? Expanding mutational and clinical spectra of the PTEN hamartoma tumour syndrome. *J Med Genet* 2004; 41: 323–326.
2. Estey E, Dohner H. Acute myeloid leukaemia. *Lancet* 2006; 368: 1894–1907.
3. Lopez-Terrada D. Integrating the diagnosis of childhood malignancies. *Adv Exp Med Biol* 2006; 587: 121–137.
4. Kleihues P, Louis DN, Scheithauer BW, et al. The WHO classification of tumors of the nervous system. *J Neuropathol Exp Neurol* 2002; 61: 215–225; discussion 226–229.
5. Hartmann C, Mueller W, Lass U, Kamel-Reid S, von Deimling A. Molecular genetic analysis of oligodendroglial tumors. *J Neuropathol Exp Neurol* 2005; 64: 10–14.
6. Hartmann C, Mueller W, von Deimling A. Pathology and molecular genetics of oligodendroglial tumors. *J Mol Med* 2004; 82: 638–655.
7. Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 2006; 24: 2707–2714.
8. McDonald JM, See SJ, Tremont IW, et al. The prognostic impact of histology and 1p/19q status in anaplastic oligodendroglial tumors. *Cancer* 2005; 104: 1468–1477.
9. Chen HY, Yu SL, Chen CH, et al. A five-gene signature and clinical outcome in non-small-cell lung cancer. *N Engl J Med* 2007; 356: 11–20.
10. Wu Y, Luo Y. Transgenic C. elegans as a model in Alzheimer's research. *Curr Alzheimer Res* 2005; 2: 37–45.
11. Kretzschmar D. Neurodegenerative mutants in Drosophila: a means to identify genes and mechanisms involved in human diseases? *Invert Neurosci* 2005; 5: 97–109.
12. Tesson L, Cozzi J, Menoret S, et al. Transgenic modifications of the rat genome. *Transgenic Res* 2005; 14: 531–546.
13. Games D, Buttini M, Kobayashi D, Schenk D, Seubert P. Mice as models: transgenic approaches and Alzheimer's disease. *J Alzheimers Dis* 2006; 9: 133–149.
14. Becich MJ. The role of the pathologist as tissue refiner and data miner: the impact of functional genomics on the modern pathology laboratory and the critical roles of pathology informatics and bioinformatics. *Mol Diagn* 2000; 5: 287–299.
15. Oosterhuis JW, Coebergh JW, van Veen EB. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer* 2003; 3: 73–77.
16. Kaiser J. Court decides tissue samples belong to University, not patients. *Science* 2006; 312: 346.

DOI:10.1002/MSJ

Network Analysis of FDA Approved Drugs and their Targets

Avi Ma'ayan, Ph.D., Sherry L. Jenkins, M.S., Joseph Goldfarb, Ph.D. and Ravi Iyengar, Ph.D

Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, New York, New York

Abstract

The global relationship between drugs that are approved for therapeutic use and the human genome is not known. We employed graph-theory methods to analyze the Federal Food and Drug Administration (FDA) approved drugs and their known molecular targets. We used the FDA Approved Drug Products with Therapeutic Equivalence Evaluations 26th Edition Electronic Orange Book (EOB) to identify all FDA approved drugs and their active ingredients. We then connected the list of active ingredients extracted from the EOB to those known human protein targets included in the DrugBank database and constructed a bipartite network. We computed network statistics and conducted Gene Ontology analysis on the drug targets and drug categories. We find that drug to drug-target relationship in the bipartite network is scale-free. Several classes of proteins in the human genome appear to be better targets for drugs since they appear to be selectively enriched as drug targets for the currently FDA approved drugs. These initial observations allow for development of an integrated research methodology to identify general principles of the drug discovery process. ***Mt Sinai J Med 74:27–32, 2007.*** © *2007 Mount Sinai School of Medicine*

Key Words: FDA drugs, network analysis, graph-theory, Systems Biology, Orange Book, drug discovery.

Address Correspondence to:

Ravi Iyengar
Department of Pharmacology
and Systems Therapeutics
Mount Sinai School of Medicine
Box 1215
One Gustave L. Levy Place
New York, NY 10029
Email: ravi.iyengar@mssm.edu

Introduction

Drug discovery is an empirical process. In spite of the enormous successes over the past 50 years in the discovery and use of therapeutic agents, it is often not clear why some drugs work and others have limited utility, with adverse effects that become apparent only after extensive use. Developing analytical methods that facilitate the discovery of some of the general rules for discovering targets for therapeutic agents, and the effects of drug-target interactions, both beneficial and adverse, would be valuable in moving the drug discovery process forward. For this effort, the field of Systems Biology and network sciences could be useful.

Systems Biology is an emerging interdisciplinary science that integrates biochemistry and cell-biology with genetics and physiology, as well as bioinformatics and computational biology to obtain holistic descriptions of biological systems at the cellular, tissue/organ and organismal levels. Operationally, such descriptions are obtained by tightly combining multivariable experiments and computational modeling to develop global views of dynamics at various scales of organization and across scales. Such integrated operational approaches are made possible due to advancements in experimental techniques, which allow the capture of the state of many cellular components at once. Computational methods and tools have greatly enabled advances in Systems Biology. The dramatic reduction in the cost of hardware, the continuing advances in applied mathematics that contribute to new algorithms, and the rapid pace of new software and database development, as well as the broadband networks that greatly facilitate access to the new databases and software, all contribute to the emergence of Systems Biology as a powerful new discipline. One of the promises Systems Biology brings is our ability to better understand cellular, tissue and organ

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20002

© 2007 Mount Sinai School of Medicine

behavior at the molecular level. This understanding could lead to better drug design, multidrug treatments, side-effect predictions, and rapid drug targeting and development as well as biomarker discovery.

Currently, the most comprehensive knowledge about the functional characteristics of cellular components is qualitative. Hence, graph-theory, a field of mathematics applied to, and developed within, the fields of sociology and computer-science has been used to analyze regulatory networks within cells[1,2,3]. Here, cellular components, such as proteins and metabolites, are represented as nodes, and their interactions represented as links. This consideration results in directed or undirected graphs (networks). These networks can be analyzed using different algorithms that provide organizational information about the system from a top-down view. Most commonly, cellular regulatory networks such as cell signaling and gene regulation systems are abstracted to directed networks. These networks, if understood from a global perspective, could, in conjunction with molecular mechanisms, help explain the origins of phenotypic behavior, and explain how this behavior changes in disease states and is restored by drug treatment. The construction of networks may allow us to see how information from initial drug-target interactions affects many components and interactions in regulatory networks within mammalian cells to alter the disease state. To construct such a network, Food and Drug Administration (FDA) approved drugs can be considered nodes and their drug-target interactions as links. At first, this bipartite network of drug-target interactions can be analyzed.

We developed a bipartite network of FDA approved drugs and their targets. We conducted statistical analyses to obtain a description of this network. Analysis of the targets using Gene Ontology indicates that certain functional classes of proteins may be "better" drug targets. This approach is a promising direct method to connect pharmacology and computational graph-theoretical Systems Biology, but it surely has limitations. For example, many drugs share the same therapeutic target but have known differential effects. These may be due to differential distribution within the body or differential interactions with as yet unidentified targets. These would not be captured easily with this approach. We summarize the limitations of graph-theoretical approaches and suggest initial metrics to handle the inherit complexity.

Analysis of the FDA's Electronic Orange Book

The FDA Approved Drug Products with Therapeutic Equivalence Evaluations 26th Edition Electronic Orange Book (EOB)[4] lists 11, 706 approved prescription drugs (RX) with therapeutic equivalence evaluations, 390 approved over-the-counter (OTC) drugs, and a list, containing 8820 approved products that have been discontinued. We excluded discontinued drugs from further analysis. Many drug products use the same active ingredients. We found 1323 unique active ingredients in all the OTC and RX drug products listed in the FDA's Orange Book. Many drug products use multiple active ingredients. Figure 1 shows a histogram of the distribution of active ingredients in FDA approved drug products. This distribution fits an exponential with the majority of drugs containing a single active ingredient, and only three drugs containing eight active ingredients. Each entry in the EOB also lists the date of approval. Figure 2 shows the addition of new active ingredients approved by year. The rate of approval of new active ingredients has a uniform distribution with an average of 33.5 drugs per year, and a high standard deviation of 10.4. Over the past 10 years there has been more fluctuation in the approval rate with peaks in years 1996 and 2000 (66 in 1996, and 53 in 2000). Since we eliminated all discontinued drugs from the analysis, we indicate the number of approved drugs per year that are still available. Drugs approved since 1983 and subsequently discontinued will alter the distribution somewhat.

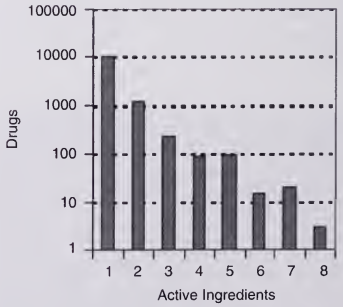


Fig 1. Number of active ingredients in each drug record listed in the FDA's Orange Book.

DOI:10.1002/MSJ

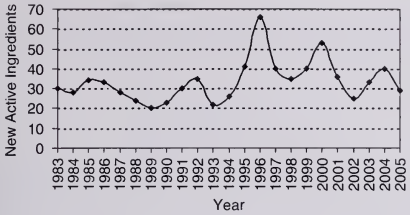


Fig 2. Number of newly approved active ingredients since 1983. Note that 528 were approved before 1983 but the information about their distribution is not provided in the Orange Book. Since discontinued drugs were removed from this analysis, the number of approved drugs per year is the number of those drugs that are still available.

Linking FDA approved drugs to DrugBank

Recently, Wishart *et al.*[5] developed a web-based resource database called DrugBank, containing many FDA approved drugs and some of their known targets. Our aim was to map FDA approved drugs and their active ingredients with known human gene targets. We extracted from the DrugBank database most drug-target interactions resulting in a network made of 1052 drugs targeting 485 proteins. The resultant bipartite network (the network has only two layers made of drugs and targets) contains 1537 nodes and 1815 interactions extracted from 2240 research articles (Fig. 3). Since the network is made of presumably, isolated drug-target interactions, we wanted to see whether these interactions are linked to form high order clusters. For this we identified islands in the network. Islands are isolated clusters of connected nodes in a network separated from other parts of the network. Island analysis found that the drug-target bipartite network contained 179 islands, with a single giant connected island made of 481 nodes (drugs and targets) (Fig. 4). The connectivity distribution of this network best fits a power-law (Fig. 5). Using this database, we linked the list of active ingredients extracted from the FDA's Orange Book to their listed molecular targets. From the list of 1471 approved unique active ingredients extracted from all the drugs listed in the FDA's orange book, we were able to find 783 matching entries in the DrugBank database. Out of these 783 active ingredients, 710 had at least one human protein target.

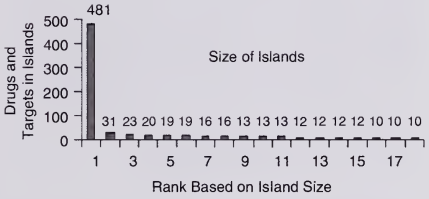


Fig 4. One hundred seventy nine islands were found in the drug-target bipartite network containing a single giant connected island made of 481 nodes (drugs and targets).

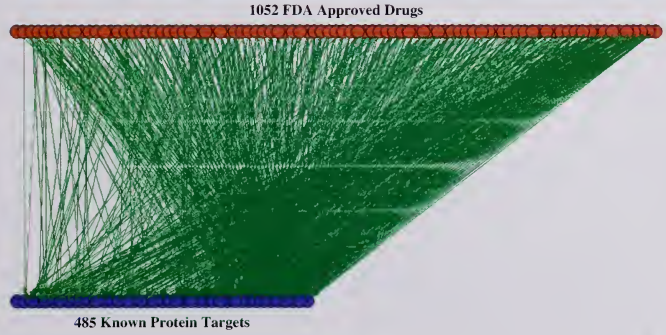


Fig 3. Visualization of the bipartite drug-target network extracted from DrugBank. Orange nodes represent drugs and blue nodes are known biomolecular targets. The network is made of 1537 nodes (1052 drugs and 485 targets) and 1815 interactions extracted from 2240 research articles.

DOI:10.1002/MSJ

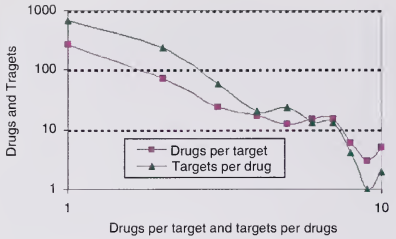


Fig 5. Distribution of drug-target interactions in a bipartite network created from DrugBank.

GO and Drug Category Analysis of the Targets

To understand the functional capabilities of drug targets we applied Gene Ontology analysis of the proteins constituting the drug targets group. We downloaded the reference file for human protein annotations from EMBL-EBI GOA Human version 44.0 from the following URL: ftp://ftp.ebi.ac.uk/pub/databases/GO/goa/HUMAN/gene_association.goa_human.gz and then matched the 485 target gene names extracted from DrugBank to their gene ontology[6] terms using AmiGO[7]. The targets are enriched in GO terms for membrane proteins, receptors, transcription factors and cell signaling components (Fig. 6).

Linking the Targets to a Consolidated Protein-protein Interaction Network

We are now developing an integrated database of mammalian interactions from several publicly available databases containing tens of thousands of interactions. From this interaction network we will identify human proteins that are drug targets. Seeing how targets and pathways are linked and interact with one another may be useful in developing further insights into the human drug-responsome.

Limitations

It is doubtful whether the graph-theory analysis and data described here can be used to predict side effects. In this qualitative analysis we used available targets, which tend to be therapeutic targets. With just that information, every member of a family of drugs with only one defined target will have indistinguishable potential effects. For example, if HMG-CoA reductase is the target, then lovastatin, pravastatin, atorvastatin, simvastatin, and rosuvastatin are nodes with arrows directed to HMG-CoA reductase. From a simple graph-theory view, these different drugs will cause identical patterns. However, we need to consider a number of additional specifications such as (1) pro-drug status: the need for metabolism to activate the drug; (2) interaction parameters with the target enzyme, e.g. the Ki may be different; (3) some differences among these drugs may be due to their binding to other targets which are not currently well defined, and may not be simply due to reduction in cholesterol synthesis, e.g. lovastatin, but not pravastatin, blocks leukocyte function antigen 1-mediated lymphocyte adhesion[8]; (4) even when multiple drugs have the same molecular target, they might have different tissue distribution because of differences in physical properties such as lipid solubility; (5) the current analysis is most likely to involve only the parent drug or the active moiety derived from a prodrug, and not its other metabolites, which could have pharmacological actions similar to or different from the parent drug.

So while graph-theoretical analysis may potentially be able to predict some differential adverse

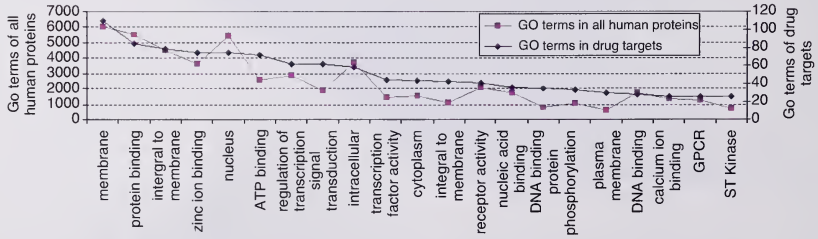


Fig 6. Gene ontology repeated terms counted for all the drug targets versus repeated terms counted for all human proteins reveal enrichment in receptors, signal transduction components, and transcription factors.

DOI:10.1002/MSJ

Table 1. Active ingredients can cause adverse effects through 12 different scenarios. The precursor, the active drug, or drug metabolites resulting from chemical processing of the drug, can interact with the intended target but cause the target to initiate undesired effects (scenarios 1, 5 and 9). The three possible different forms of the drug can interact with other unknown or undesired targets in the same cell type (scenarios 2, 6 and 10) or different cell types (scenarios 4, 8 and 12). Also, the three possible different forms of the drugs can cause unwanted effects by targeting the intended target but in the unintended cell type (scenarios 3, 7 and 11).

	Same cell same target	Same cell different target	Different cell same target	Different cell different target
Drug precursor	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Active drug	Scenario 5	Scenario 6	Scenario 7	Scenario 8
Drug metabolites	Scenario 9	Scenario 10	Scenario 11	Scenario 12

effects of drugs working on different defined targets, it appears that within a class of drugs with the same therapeutic target simple graph-theoretical analysis will be insufficient. Quantitative modeling analysis, in conjunction with network analyses, may be required. Table 1 summarizes different combinatorial scenarios involving parent drug, metabolites, targets and tissues that may contribute to differential effects of drugs within a therapeutic class. If multiple drugs with varying potencies or efficacy interact with the same target, as is the case with the statins, then the combinatorial complexity described in Table 1 will increase. An additional problem arises in the classification of targets. For example, the DrugBank database is incomplete in terms of drug targets. In many cases the existence of multiple targets is included in descriptive material but these targets are not listed in the database. In some cases it appears that the decision was made to include only targets with presumed therapeutic actions and omit those primarily associated with adverse effects. In other cases an argument can be made that some of the omitted targets may be involved in therapeutic effects as well. For example, the listing for the tricyclic antidepressant amitriptyline, includes only the norepinephrine and serotonin transporters as targets. It does not list histamine H1 receptors, at which amitriptyline is more potent than as an uptake blocker, or muscarinic receptors, which contribute to amitriptyline's side effect profile[9]. The listing for the alpha/beta adrenergic antagonist carvedilol lists alpha-1 and beta-1 receptors but not beta-2 receptors. Carvedilol is essentially a nonselective beta blocker with similar Ki for human beta-1 and beta-2 receptors[10]. For the anti-muscarinic drug atropine, all five muscarinic receptors are listed as targets, but for the anti-muscarinic oxybutynin only the M1 receptor is listed, although oxybutynin has similar affinity for M3 and M4 receptors[11]. And as a final example, the only target listed for the antiarrhythmic drug quinidine is the voltage-gated sodium channel, although this drug has long been known to block potassium-channels[12]. This action is a major contributor to the prolongation of cardiac action potential duration produced by quinidine, and its increased probability of producing the arrhythmia torsade de pointes compared to selective sodium channel blockers. These limitations are described not as a criticism of DrugBank, which is a very valuable initial effort for the pharmacology research community, but to highlight the complex issues that will require further reasoning to develop rules for database and network development.

Conclusions

Our initial attempt to develop a network to understand the connectivity between FDA approved drugs and their targets, and how these targets themselves cluster, is preliminary but has many potential uses. Lamb *et al.*[13] have recently mapped microarray signature patterns after application of FDA approved and other drugs to cancer cell-lines with the goal of identifying similarities and differences among the effects induced by the different drugs. Their approach treats cells as black boxes. The drugs are the inputs and the gene expression patterns are the output. Our ability to link drugs to their targets and the targets to a network of protein interactions and signaling networks may lead us to understand the internal configuration of the black box in between the drug target(s) and their effects, such as gene expression patterns. We hope to be able to connect phenotypes induced by different drugs to the regulatory patterns and molecular mechanisms that lead to changes in gene expression patterns. This understanding could lead to the identification of new multidrug treatments, side-effect prediction, and the discovery of new drug targets.

DOI:10.1002/MSJ

References

1. Albert R. Scale-free networks in cell biology. *J Cell Sci* 2005; 118(Pt 21): 4947–4957.
2. Ma'ayan A, Blitzer RD, Iyengar R. Toward predictive models of mammalian cells. *Annu Rev Biophys Biomol Struct* 2005; 34: 319–349.
3. Ma'ayan A, Iyengar R. From components to regulatory motifs in signalling networks. *Brief Funct Genomic Proteomic* 2006; 5(1): 57–61.
4. U.S. Food and Drug Administration/Center for Drug Evaluation and Research: Approved Drug Products with Therapeutic Equivalence Evaluations Orange Book http://www.fda.gov/cder/orange/default.htm.
5. Wishart DS, Knox C, Guo AC, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res* 2006; 34: D668–D672.
6. Harris MA, Clark J, Ireland A, et al. Gene Ontology Consortium. The Gene Ontology (GO) database and informatics resource. *Nucleic Acids Res* 2004; 32: D258–D261.
7. Gene Ontology Consortium. The Gene Ontology (GO) project in 2006. *Nucleic Acids Res.* 2006; 34: D322–D326.
8. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nat Med* 2001; 7(6): 687–692.
9. Richelson E. Tricyclic antidepressants and histamine H1 receptors. *Mayo Clin Proc* 1979; 54(10): 669–674.
10. Smith C, Teitler M. Beta-blocker selectivity at cloned human beta1- and beta2-adrenergic receptors. *Cardiovasc Drugs Ther* 1999; 13(2): 123–126.
11. Moriya H, Takagi Y, Nakanishi T, et al. Affinity profiles of various muscarinic antagonists for cloned human muscarinic acetylcholine receptor (mAChR) subtypes and mAChRs in rat heart and submandibular gland. *Life Sci* 1999; 64(25): 2351–2358.
12. Yao JA, Trybulski EJ, Tseng GN. Quinidine preferentially blocks the slow delayed rectifier potassium channel in the rested state. *J Pharmacol Exp Ther* 1996; 279(2): 856–864.
13. Lamb J, Crawford ED, Peck D, et al. The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease. *Science* 2006; 313(5795): 1929–1935.

DOI:10.1002/MSJ

Handwashing and Infection Control

Fred Rosner, MD, MACP

Department of Medicine, Mount Sinai Services at Elmhurst Hospital Center, Elmhurst, New York
Professor of Medicine, Mount Sinai School of Medicine, New York, New York

Introduction

The hands of healthcare workers are the most common mode of transmission of pathogens to patients because most healthcare workers such as physicians and nurses fail to wash their hands before and after touching a patient. Proper hand hygiene can prevent health care-associated infections and the spread of antimicrobial resistance.[1] The authors list certain factors that contribute to poor compliance with hand hygiene, including poor access to handwashing facilities such as sinks, the time required to perform standard handwashing, irritant contact dermatitis associated with frequent use of soap and water, high workloads for the healthcare workers, knowledge deficits among healthcare workers, and the failure of healthcare facility administrators to make hygiene an institutional priority.[1] The authors conclude that scientific evidence and ease of use support the use of alcohol-based hand rubs for hand hygiene during patient care and contacts.[1] The alcohol rub technique, the authors further conclude, is microbiologically more effective, more accessible, less likely to cause problems and saves time and human resources.[1] Finally, the authors conclude that there is substantially better adherence to hand hygiene with alcohol rub than with handwashing and it should become the standard for hand hygiene in healthcare facilities and settings.[1]

Brief Literature Review

Device utilization in critically ill patients is responsible for a high risk of complications such as catheter-related bloodstream infections, ventilator-associated pneumonia and urinary tract infections.[2] Antiseptic-coated catheters may reduce catheter-related infections, but this hypothesis requires further confirmation.[2]

The authors conclude with a series of recommendations to prevent or reduce device-associated infections including handwashing and other measures.[2] Corona and Raimondi review the epidemiology and preventive measures of mosocomial infections in an intensive care unit.[3] The authors state that over 80% of such infections are related to device utilization needed for patient life support. The authors make a series of recommendations to reduce or prevent such infections, including the use of multi-use, closed system suction catheters, lubrication of the endotracheal tube cuff with a water-soluble gel and other measures.[3] The authors conclude that the use of these measures may reduce morbidity and mortality in ICU patients who need devices for life support.[3] Collins and Hampton conclude that effective handwashing, including drying, is recognized as a critical factor in infectic control. "Handwashing is not always undertaken as it should be".[4] The authors recommend that ways of promoting hand hygiene and ways of ensuring that healthcare workers follow hygienic guidelines must be found.[4] In a very lengthy review with over six hundred references, Kampf and Kramer quote the CDC guidelines that hygienic hand disinfection with an alcohol-based hand rub is the preferred method to be used after patient care activities, including wound dressing.[5] Handwashing is also indicated after using the restroom and after blowing the nose and other situations of risk of spreading microorganisms.[5] Tiaki discusses handwashing rituals and regimes in practice and states that handwashing is a basic nursing task and a profoundly important aspect of nursing practice. Done well, concludes the author, it can greatly reduce the risk of infection. Done badly, it can severely compromise patient care.[5]

Jonathan Katz states that the importance of thorough handwashing for protection against various types of infection has been known since early

Address Correspondence to:

Fred Rosner
750 Elvira Avenue
New York, NY 11691.

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20003

© 2007 Mount Sinai School of Medicine

recorded history.[6] He tabulates the indications for handwashing and the recommended hygienic techniques. The author concludes that handwashing is considered the single most important intervention for prevention of nosocomial infection in patients and healthcare workers. Unfortunately, states the author, compliance with standard protocols for hand hygiene in the health care environment is generally poor. The author strongly recommends that the Guidelines issued by the CDC in 2002 for hand hygiene in the healthcare setting[7] be adopted.[6] Thomas Kovach describes a program which provides detailed workshops covering handwashing and infection control.[8] These workshops are conducted by qualified infection control nurses and are accredited by the American Nursing Association.[8] Umbilical cord infections are also a problem in many developing countries. Mulhany and his colleagues discuss the problem at some length and offer recommendations to reduce or prevent such infections.[9] Their review is comprehensive and very informative.[9] Muller and McGeer discuss febrile respiratory illness in the intensive care unit setting and provide guidelines for standard precautions including handwashing and other measures.[10]

Handwashing in Jewish Law

Judaism requires handwashing in a variety of situations for hygienic, ethical, legal, moral and spiritual reasons. For example, in the morning upon arising from sleep, one is required to wash one's hands and recite a blessing. After using the restroom, one must wash one's hands and recite a blessing.

Before and after a meal, a biblical commandment requires Jews to wash their hands and recite a blessing over the handwashing and over the food, which God has provided for us.

Before the priestly blessing can be offered, the Priests (Kohanim) must wash their hands. When the Temple was functioning in Jerusalem, the Priests had to wash their hands and feet before performing their temple service. On the Day of Atonement (Yom Kippur), the High Priest has to wash not only his hands and feet but immerse his whole body in a ritual bath five times during the day as he performs the ritual service. If a Jew touches or lifts or carries a ritually unclean object such as a corpse or part of a corpse or skeleton, he is obliged to cleanse himself by immersion in a ritual bath. Thus, Jewish Law requires handwashing for a variety of hygienic and religious reasons in different situations.

Discussion and Summary

The hands of healthcare workers are the most common mode of transmission of pathogens to patients because most healthcare workers such as physicians, nurses, technicians, therapists and others fail to wash their hands before and after patient contact.[1] Many factors account for this noncompliance with standard hygienic principles, including personal resistance by the healthcare worker, lack of access to handwashing facilities such as sinks, contact dermatitis from frequent contact with soap and other cleansing agents, lack of administrative support for providing clinical hygiene facilities, policies, and other reasons, none of which are insurmountable. Recent evidence suggests that alcohol swabs may be just as or even more effective than handwashing and are certainly more convenient. Many authors recommend them highly.

Particular attention must be paid to hygiene in an ICU setting or wherever devices are needed and used for life supporting patient care.

Conclusion

Infection control by handwashing and other methods have come a long way in the past few decades but some problems are not yet solved. Macias and Ponce-de-leon focus on these problems and on the new challenges for infection control because of the ever-growing number of immunocompromised patients and the occurrence of new infections such as SARS and the avian flu epidemic.[11] The authors conclude that infection control by handwashing and other methods is still under consideration due to the introduction of new and sophisticated invasive procedures dictated by "scientific developments which are changing the face of medicine".[11] We need a new and vigorous commitment to our patients, conclude the authors. "To prevent, educate and train" is too vague, continue the authors. To be fair and honest with our patients, the authors finally conclude, we must establish specific points for initial action for hospitals without a tradition of infection control, as the authors tabulate for the reader.[11]

Acknowledgments

The author is indebted to Mrs. Miriam Rodriguez for typing the manuscript and to Librarian Mrs. Ruth Hoffenberg for providing the reference material.

DOI:10.1002/MSJ

References

1. Trampuz A, Widmer AF. Han hygiene: a frequently missed lifesaving opportunity during patient care. *Mayo Clin Proc* 2004; 79: 109–116.
2. Degaudio A, DiFillippo A. Device-related infections in critically ill patients. *J Chemother* 2003; 15(5): 419–427, (Florence, Italy).
3. Corona A, Raimondi F. Prevention of nosocomial infection in the ICU setting. *Minerva Anesthesiol* 2004; 70(5): 329–337.
4. Collins F, Hampton S. Hand-washing and methicillin-resistant staphylococcus aureus. *Br J Nurs* 2005; 14(13): 103–107.
5. Kampf G, Kramer A. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. *Clin Microbiol Rev* 2004; 17(4): 863–893.
6. Katz JD. Hand washing and hand disinfection: more than your mother taught you. *Anesthesiol Clin: Clin North America* 2004; (22): 457–471.
7. Boyce JM, Pittet D. Guidelines for hand hygiene in health care settings. Recommendations of the Healthcare. Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force Society for Healthcare epidemiology of America/Association for Professionals Infection Control/Infections Diseases Society of America. *Morb Mortal Wkly Rep* 2002; 51: 1–45.
8. Kovatch TL. Freedom from the chain of Septic flow: hand washing in infection control. *J Pract Nurs* 2005; 55(4): 10–15, Winter.
9. Millany LC, Darmstadt GL, Telsch JM. Role of antimicrobial applications to umbilical cord in neonates to prevent bacterial colonization and infection: a review. *Pediatr Infect Dis J* 2003; 22(11): 996–1002.
10. Muller MP, McGeer A. Febrile respiratory illness in the intensive care unit setting: an infection control perspective. *Curr Opin Crit Care* 2006; (12): 37–42.
11. Macias AE, Ponce-de-Leon S. Infection Control: old problems and new challenges. *Arch Med Res* 2005; (36): 637–645.

DOI:10.1002/MSJ

Job of the Bible: Leprosy or Scabies?

Thierry Appelboom, MD, PhD,[1] Elie Cogan, MD, PhD,[2] and Jean Klastersky, MD, PhD[3]

[1]Division of Rheumatology and Physical Medicine, Hôpital Erasme, Université libre de Bruxelles, Brussels, Belgium
[2]Department of Internal Medicine, Hôpital Erasme, Université libre de Bruxelles, Brussels, Belgium
[3]Department of Internal Medicine, Institut Bordet, Brussels, Belgium

Abstract

Proposing a medical diagnosis *a posteriori* of a person who died a long time ago is not as impossible as it sounds if sufficient medical history is available.

A whole book of the Bible is devoted to Job and his trials. The diagnosis of leprosy has been generally accepted by medieval commentators because the verses of the Book speak of ulcers disseminated over the skin, and also because leprosy is an exemplary sanction imposed by way of example by God to punish those who have committed a sin.

In this paper, we have taken the different verses with a medical content from the Book of Job, and reconstructed the clinical picture as if the patient had turned up in the 21st century in order to see if the diagnosis of leprosy may be called into question, and to discuss the limits of the medico-historic approach.

The clinical picture of the disease consists of deterioration in the general condition, with widespread pain, confusion, skin eruptions, bilious vomiting, and so on.

Under these conditions, if Job did exist, and if the retrospective medical history is reliable, the most likely diagnosis is that of scabies rather than leprosy. ***Mt Sinai J Med 74:36–39, 2007.*** © *2007 Mount Sinai School of Medicine*

Key Words: Job, medical history, retrospective diagnosis.

Address Correspondence to:

Thierry Appelboom
Division of Rheumatology and
Physical Medicine
Erasmus Hospital
808 route de Lennik B-1070
Brussels, Belgium
Email: tappelbo@ulb.ac.be

Introduction

A whole book of the Bible is devoted to Job and his trials, as a testimony to the importance of his life and experiences.[1] He asked fundamental questions, rather than accepting readymade answers based on traditional authority. He represents a break in Biblical thought.[2]

In his Book, Job is happy about everything; he venerates God, showering him with offerings. And in all respects, his life is an example of piety until the point at which God decides to put him to the test and allows Satan to inundate him with misfortunes and suffering, all his wealth disappears; his children die; Job himself is struck down with "leprosy" and finds himself abandoned on a dung heap where patients branded by malediction await death.[3] His faith enables him to bear all his torment and in the end, God sends his blessing upon him.[1] The diagnosis of leprosy has been generally accepted by medieval commentators (malignant ulcer for the Syrian, Greek, and Hebraic tradition) because the verses of the Book speak of ulcers disseminated over the skin, also because leprosy is an exemplary sanction imposed by way of example by God to punish those who have committed a sin.[3,4]

But since the term leprosy covered a series of skin diseases, should the diagnosis of leprosy be revised?

It would not be impossible to make a retrospective diagnosis of Job's ailment if images of the person existed at the time when he is thought to have lived.

But with rare exceptions such as the Synagogue at Doura Europos, the first representations of Biblical persons date only from the end of the Middle Age.

Later on, the Book of Job was included in the Vulgate, and Christian artists made but not as many representations of Job as their imaginations gave them leave.[5,6]

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20008

© 2007 Mount Sinai School of Medicine

Fig 1. A Flemish picture dating from the 17th century representing Job (as the artist imagines him) covered in and suffering from skin problems; erythema, excoriated vesicles, areas of necrosis with seropurulent discharge, and so on. Consistent with erythema multiforme? Courtesy of the Museum of Medicine of Brussels.

In this paper, we have taken the different verses with a medical content from the Book of Job, and reconstructed the clinical picture as if the patient had turned up in the 21st century in the Emergency Room of a general hospital with his symptoms and clinical signs, in order to see if the diagnosis of leprosy may be called into question, and to discuss the limits of the medico-historic approach.[1,7]

The Clinical Picture

A patient of about 50 years of age, of Middle-Eastern origin, presents in the Emergency Room of a general hospital for nonlocalized pain and changes in his general condition; he is accompanied by his wife who urges him to rely on divine mercy, and by three friends who keep telling him that he deserves his fate and that suffering is a punishment and a means of purification.

Medical History

Those accompanying him inform us that until recently, he lived in the country surrounded by his seven sons and three daughters, that he had a large cattle ranch which he managed with the help of numerous employees. His life style was described as comfortable. Recently, while he was away, his house collapsed and his children perished in the fire. This came as a great blow to him. Since then, he has been very depressed and is haunted by the thought of his death (Job I; 1 and X;1).

For 7 days and nights before he was brought to the hospital, he was being woken up by severe pain (XIV; 22) and at night especially, by pain in his bones (XXX; 17). He then discovered skin lesions from the soles of his feet to the top of his head. These sores progressively ulcerated (II;7 and 13).

His general condition then rapidly deteriorated.

At present, he complains particularly of dorso-lumbar pain and in particular, of skin ulcers that are so itchy he is scratching himself with a sliver of broken glass (II; 8), and, in his words, his body is rotting as he lies there. He is also vomiting large quantities of bile (cholemesis?)(VII; 5 and XVI; 13) and the vomit is sometimes bloody (XVI; 18).

Physical Examination

The Emergency Room doctor observes that the patient is depressed and very wasted (the bones are protruding) (XIX; 20 and XXX; 30); he is wrinkled and appears older than his age (XVI; 8); his face is very emaciated and looks gray (XVI; 16); his cranium is balding (this seems to be a recent problem) (I; 20); he trembles now and then particularly when he is talking (XXI; 6); his pulse is strong and rapid (XXI; 6 and XXX. 17); his eyelids are a deathly color (XVI. 16). His breath is fetid (XIX; 17).

Ulcerated lesions cover his whole body; they are painful when touched; some of them are purulent (as if there were worms) and others have a crust (VII; 5).

DOI:10.1002/MSJ

Cracked skin is also noted (VII; 5). In some places, the skin has become black (XXX; 30).

Several centuries later, artists tried to represent his condition; he is depicted as aged, thin, vexed or imploring the heavens, with protuberant bones, bearded, bald or the hair standing on end in terror, and exceptionally covered with ulcers that ooze blood.

After his examination, the patient insisted on leaving and disappeared.

Some weeks later, the hospital learned that he had recovered and was leading an untroubled life.

Discussion

What is the diagnosis that can be made? The clinical picture of the disease consists of deterioration in the general condition, with widespread pain, confusion, skin eruptions, and bilious vomiting. More specifically, the decline in the general condition was progressive, then was recently aggravated. The pain is not confined to one area but preferentially localized in the lumbar region. The mental confusion is characterized by agitation interspersed with calmer periods, hallucinations and also by coherent discourse.

The skin condition is dominated by prurient and/or ulcerous lesions with exudates (superinfection?), crusts, cracks, etc. and no part of the body is spared; to these main symptoms are added bilious vomiting, tachycardia, a greyish hue, and a significant weight loss. *A priori*, the patient does not seem to have a temperature (verses XXX; 30) and the condition healed "spontaneously".

The diagnosis of leprosy adopted to begin with may be considered questionable because the skin lesions of leprosy are neither pruritic nor painful (in the area affected, a loss of sensitivity to heat and pain is noted), are complex and spontaneous healing is exceptional; moreover the Hebrew term for leprosy ("Tzara'ath") encompasses a range of conditions of the skin.

In the Biblical sense, leprosy is described as a swelling of the skin, with a crust, a whitish patch, whose severity may be evaluated by the depth of the skin affected, which is not related here.

Parenthetically, according to certain commentators, the malignant ulcers covering Job from foot to head might be Nisle Ulcer mentioned in Deuteronomy (XXVIII 28;27), or given its gravity, tuberculoid leprosy.[4,7,8]

"Job's syndrome" is improbable; although immune deficiency is complicated by secondary skins superinfections, as the condition is genetic it is not curable. Patients suffering from Job's syndrome have a protuberant forehead, deep-set eyes, an enlarged nose, thickened lower lip and ears that are not reported here; nevertheless the physical deformities were clearly identified by the Hebrews because they forbade people with them access to and service in the Temple.

Disseminated pustular psoriasis, generalized vaccinia, and pyoderma gangrenosum are not excluded.

In a patient who raised animals, an infectious disease such as vaccinia is possible, but vaccinia lesions are not pruritic.

A clinical picture associating dementia and dermatitis can be explained by a lack of vitamin PP, thus suggesting pellagra, but this excludes diarrhea.

The condition may also be caused by a reactive depression following the brutal death of several members of his family which might have led to him giving up, leading to severe weight loss and even vitamin deficiency.

The personality of the patient is not known, but at this stage, the skin lesions and the behavioral problems with hallucinations present a condition mimicking a disease state possible.

The skin condition could also fall within the bounds of a systemic condition such as spontaneously resolving vasculitis. The depressive condition might have led the patient to partake of opium (in the form of a poppy extract) or cannabis, which could have made him agitated, and it is known that these substances, in particular, if they are not pure, may cause the complication of arteritis which affects the extremities and gets progressively worse over time.

The possible hypothesis of a cancerous condition with metastases in the bone, leading to lumbar pain, and complicated by an acute systemic picture merits consideration but seems improbable when you consider the subsequent favorable outcome.

Micro-angiopathic anemia, fungal infections, and septicemia could also explain the hyperacute picture.

Finally, the best explanation of the skin condition central to the clinical picture may be a parasitic infestation due to scabies; in this case, the lesions are very pruritic, particularly in the night, small in size, papuliferous, even erythematous, with occasionally a small canal that is difficult to locate; scabies may become eczematous or infected. The ulcers, the pruritis, the need to scratch himself, and the favourable outcome are all elements that suggest this diagnosis.

In conclusion, if the retrospective medical history is reliable, the most likely diagnosis is that of scabies.

DOI:10.1002/MSJ

The Book of Job is important in the monotheist tradition, as it evokes the problem of evil and the attitude of God toward the misfortunes that affect the just person.

But, if Job had been struck by scabies rather than by leprosy, would the face of the world have changed?

References

1. Martin D. Bible Martin. Le Livre de Job 1744 (www.biblemartin.com).
2. Vogels W. Job, l'homme qui a parlé de Dieu. ISBN 2204051470.
3. Terrien S. Job. Commentaire de l'Ancien Testament. Editions Delachaux et Niestlé, Neufchatel (Suisse), 59.
4. Dhorme P. Le Livre de Job. Librairie Victor Lecoffre, rue Bonaparte, 90 Paris, 1926; 16–18.
5. Chouraqui A. La vie quotidienne des Hébreux au temps de la Bible. Editions Hachette, Paris 1971; 163–167.
6. Larcher C. Le Livre de Job. In: Encyclopédie Catholicisme. Editeur Letouzey et Ané, Paris 1967; 900–908.
7. Le Livre de Job traduit par RP Larcher, O.P. Editions du Cerf (Paris), 1950.
8. Steinmann J. Le Livre de Job; Lectio Divina 16, Editions du Cerf, Paris VII, 1955; 90–91.

DOI:10.1002/MSJ

PRISMATIC CASE

Apparent Mineralocorticoid Excess Manifested in an Elderly Patient with Hypothyroidism

Maria I. New, MD

Department of Pediatrics, Mount Sinai School of Medicine, New York, New York

Key Words: apparent mineralocorticoid excess, AME, hypothyroid.

Introduction

In 2006[1], an elderly woman with hypothyroidism was described who manifested the biochemical changes of 11β-hydroxydehydrogenase type 2 enzyme (11β-HSD2) deficiency similar to those observed in Apparent Mineralocorticoid Excess (AME) syndrome. The biochemical findings reverted to normal when thyroid treatment was administered. Molecular genetic studies did not detect a mutation in the 11β-HSD2 gene; thus the patient did not have AME, but only biochemical changes. The biochemical changes similar to 11β-HSD2 deficiency were associated with hypertension, hypokalemia, hyporeninemia, and low serum aldosterone concentration. These abnormalities were reversed with thyroid treatment.

This case is prismatic because it will change the diagnostic procedures to include biochemical studies of cortisol metabolism in hypothyroidism, a very common disorder.

Address Correspondence to:

Maria I. New
Professor of Pediatrics
Director, Adrenal Steroid Disorders Program
Department of Pediatrics
Mount Sinai School of Medicine
1 Gustave L. Levy Place
Box 1198
New York, NY 10029
Email: maria.new@mssm.edu

The presentation of AME in an elderly patient is unusual, as AME is most often found early in life[2]. AME results from the inactivation of the cortisol → cortisone shuttle (F → E shuttle), and causes severe hypertension with hypokalemia and metabolic alkalosis. Other clinical features include persistent polydipsia and polyuria, and failure to thrive. Biochemical markers include low plasma renin activity (PRA), low steroid levels including low to undetectable aldosterone and a decrease in blood pressure in response to restriction of dietary Na^+. Licorice, glycyrrhizic acid and carbenoxolone are competitive inhibitors of 11β-HSD2 activity and have been known to cause acquired AME. However, AME is most often found it its monogenic form. Over 30 mutations in the gene encoding 11β-HSD2, *HSD11B2*, causing AME have been found[3].

Case Report

Inagaki *et al.*[1] describe the case as follows:

> The patient, an 84-year-old woman, presented with hypertension and hypokalemia caused by primary hypothyroidism, and these changes were reversed by thyroid treatment. While on candesartan, her blood pressure remained elevated at 160–180/80–90 mmHg. Endocrine evaluation of her thyroid function showed increased thyroid-stimulating hormone (TSH), and decreased free thyroxine and free triiodothyronine. Ultrasonography showed an atrophic thyroid, while antithyroid peroxidase and antithyroglobulin antibodies were negative. Liver functions were normal, but serum creatinine and mean 24-h creatinine clearance showed some impairment of renal function. Sodium and chloride levels were normal, while potassium was low (2.6 mEq/l). While the patient was hypokalemic, urinary potassium excretion was very high (24.8 mEq/day). Both PRA and aldosterone were low, while adrenocorticotropic hormone (ACTH), cortisol and catecholamines were normal. The adrenals

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI:10.1002/msj.20001

© 2007 Mount Sinai School of Medicine

were found to be normal upon radiological scan. No mutations were found upon analysis of the *HSD11B2* gene, which encodes the 11β-hydroxydehydrogenase type 2 (11β-HSD2) enzyme. Other causes of AME were ruled out: ingestion of licorice and glycyrrhizic acid, ecoptic ACTH syndrome, and tumors producing deoxycorticosterone or corticosterone.

Treatment of the patient's hypothyroidism with levothyroxine sodium reversed the hypokalemia and hypertension. PRA and aldosterone levels returned to normal ranges after the F/E ratio lowered. Improvement of the patient's general fatigue and lower leg edema occurred. Finally, her blood pressure was maintained by the initial dosage of candesartan, and serum potassium levels remained normal without potassium gluconate or sprinolactone.

Discussion

Hellman *et al.* first reported in 1961 that thyroid hormone may inactivate the conversion of F to E, affecting the F $\rightarrow$ E shuttle. The altered F $\rightarrow$ E shuttle has been related to many conditions ranging from hypertension to end-stage renal disease, liver cirrhosis, intrauterine growth retardation, and preeclampsia[4]. Early thyroid hormone replacement therapy may be prudent in subclinical hypothyroid patients if hypothyroidism causes symptoms of mineralocorticoid excess resulting from changes in cortisol metabolism. Thyroid hormone's effect on cortisol metabolism may contribute to the pathogenesis of common diseases such as central obesity and idiopathic osteoporosis. In the largest study of AME patients with *HSD11B2* gene mutations in both severe[5] and mild forms[6], the patients were clinically euthyroid and the thyroid hormone axis was normal.

Conclusion

The patient in "AME manifested in an elderly patient with hypothyroidism" represents a prismatic case in which a common endocrine disorder (e.g. hypothyroidism) causes biochemical changes suggesting an acquired and treatable form of abnormal cortisol metabolism.

References

1. Inagaki K, Otsuka F, Otani H, Sato C, Miyoshi T, et al. Apparent Mineralocorticoid Excess Manifested in an Elderly Patient with Hypothyroidism. *Am J Hypertens* 2007; 20: 104–107.
2. New MI, Levine LS, Biglieri EG, Pareira J, Ulick S. Evidence for an unidentified steroid in a child with apparent mineralocorticoid hypertension. *J Clin Endocrinol Metab* 1977; 44: 924–933.
3. New MI, Geller DS, Fallo F, Wilson RC. Monogenic low renin hypertension. *Trends Endocrinol Metab* 2005; 16: 92–97.
4. Palermo M, Quinkler M, Stewart PM. Apparent mineralocorticoid excess syndrome: an overview. *Arq Bras Endocrinol Metabol* 2004; 48: 687–696.
5. Dave-Sharma S, Wilson RC, Harbison MD, Newfield R, Razzaghy-Azar M, et al. Extensive Personal Experience: Examination of genotype and phenotype relationships in 14 patients with apparent mineralocorticoid excess. *J Clin Endo Metab* 1998; 83: 2244–2254.
6. Wilson RC, Dave-Sharma S, Wei J, Obeyesekere VR, Li K, et al. A genetic defect resulting in mild low-renin hypertension. *Proc Natl Acad Sci (USA)* 1998; 95: 10200–10205.

DOI:10.1002/MSJ

INSTRUCTIONS TO AUTHORS

THE MOUNT SINAI JOURNAL OF MEDICINE: A Journal of Personalized and Translational Medicine is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and other major databases. The journal features articles on the evolving nature of clinical care, its close linkage to bio-medical research and the resulting opportunities for enhanced patient care. The Journal has published continuously since 1934 as a general medical journal for a worldwide audience, but starting January 2007, shifts its focus to **translational** and **personalized medicine**, areas of growing medical importance and interest.

All Manuscripts and Editorial correspondence should be addressed to:

Michelle Gadsden
c/o John Wiley & Sons, Inc.
111 River St., Mail Stop-8-01
Hoboken, NJ 07030
Phone: 201-748-6199
Fax: 201-748-6667
E-mail: msjm@wiley.com

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and either (3) the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in the *Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from the Journal's web site. Use additional copies of the form if there are more than six authors, and indicate the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Manuscripts must be double spaced throughout (including references, legends, and tables). The title page should designate the location(s) where the work was done, and the name and address of the corresponding author. (See also **Title Page** section below.) A separate page should be used for each table. The legends, in numerical sequence, should be typed together on one or more pages (if needed). A separate page, or pages, should list the references in the sequential order they are cited for the first time in the narrative text.

Drug names. Drugs must be identified by their generic names. Do not use abbreviations on the abstract page(s) or in legends. Define all abbreviations on first use in the body of the manuscript. All abbreviations used in a table must be defined at the bottom of the table.

Previously published material. Any figures, graphs, tables or extensive textual quotes taken directly from other sources must be accompanied by a signed statement from the author and the publisher of this material, giving **permission** to the *Journal* for reproducing it **in both print and electronic formats**.

Human and animal subjects. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If the manuscript deals with specific patients for whom identifiers (as defined by HIPAA) are provided, the consent of each patient for the release of information must accompany submission of the manuscript. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office (or its equivalent) which supervises such work.

Title Page. This page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, and middle initial(s), if any, and not more than two academic degrees; (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (as well as telephone, FAX number, and email address) of the author who will receive and respond to correspondence; (6) acknowledgments of sources of grant support; (7) name, place, and date of any conferences at which some or all of the information was presented; and (8) **a running head of fewer than 40 characters.** At the bottom of the title page, **list 3 to 10 key words or phrases** to facilitate computer searches in accord with medical subject headings from *Index Medicus*.

Abstract. All articles must include an abstract of not more than 400 words. This abstract will be published in the *Journal* with the article. Enough detail should be provided in the abstract so that it will be sufficiently informative to stand alone when placed on the *Journal*' s web page (prior to publication of the entire article in the *Journal*). Abstracts should be double spaced. Abstracts for manuscripts specifically describing original clinical and/or laboratory research should be structured in four paragraphs:

Background: what problem(s) was (were) addressed;
Methods: how the study was performed;
Results: the most significant results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page and also after the abstract to facilitate computer searches. Repeat at the end of the abstract the same key words that are listed on the title page.

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning, in conformity with the style used by the *Journal*. Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar prior to submission.

Figures. Photographs, line drawings, and graphs should NOT be embedded in the text, but as separate files. All figures must be submitted in TIFF or EPS format. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column (approximately 3 1/8"). The authors must pay attention to the quality of print reproductions of photographs, x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced

to fit the 3 1/8" width of a column. The name of the subject and hospital number(s) should not appear in the print. Black and white photomicrographs are preferred, and electron photomicrographs should have internal scale markers. Images that are to appear together as one figure should be labeled and arranged to indicate this.

If possible, avoid using a photograph that includes the face or part of the face of a subject. If that is impossible, facial features should be masked to prevent identification of the subject unless they include details absolutely essential to the text. **In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.**

Color figures. Color figures can only be published in the print journal if authors absorb the cost. Authors will be charged $500 per page of color. One or more pages of complimentary color may be granted by the Editor.

Legends. Legends should not duplicate the text. They should appear together in numerical order, double spaced, on one or more pages following the text. Number each legend to match the figure it describes. A figure composed of several images appearing together should have a single legend identifying the separate elements by position ("upper left," "middle," etc.) or by letters (A, B, C, etc.). If such figures have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification (e.g., 10X, 40X, 100X) and type of stain used for photomicrographs.

Footnotes. Footnotes are not to be used, except as noted in the sections on **Units of Measurement** and **Tables.**

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (**TABLE 1**, etc., in bold type) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text, and type the title, *in italics*, on a separate line below the table' s number. Identify all abbreviations and/or symbols used in the table in a footnote at the bottom of the table. We suggest using the Table function in Microsoft Word.

References. All references cited in the text should be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation. For example:

Cytomegalovirus (1), steroids (2, 3), and drug abuse (4-6) have all been implicated (7).

Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus* . The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled "References" are illustrated in the version of "Uniform Requirements" published in *The New England Journal of Medicine* referenced below. The list of references must be typed, double spaced, on one or more pages following the text, in the arrangement and punctuation style shown in the examples below. **The list of references should NOT be formatted as "Endnotes."**

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. *Mt Sinai J Med* 1994; **61**:99–112.
2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med* 1997; **336**: 309–315.
3. Couser WG. Glomerular diseases. In: Stein J, editor. Internal medicine. 2nd ed. Boston: Little Brown; 1987. pp. 834–861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then use "et al."

A citation to an article that has not been published in print (journal, book) and that has been obtained by accessing a Web site must include, in addition to the names of the authors and the title of the article, the DOI or Web address at which the article can be found and accessed, and the date when it was last accessed.

References to unpublished data (unless the information is in press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission.

Proofs. A revised, copy-edited proof will be sent to the corresponding author via email as soon as it is available, for necessary corrections only. All corrections should be made on this copy, which must be returned to the publisher within 48 hours.

Offprint Orders. An offprint order form will be sent to the corresponding author. If offprints are desired, the form must be returned to the editorial office with full payment. Offprints are available in multiples of 100, at a cost depending on the total number of printed pages.

Supplementary Online Material. Authors may submit supplementary material for their articles to be posted in the electronic version of the journal. There are no restrictions on file types, however please keep in mind that the more universal the file type the more accessible it will be to the community. All supplementary material must be submitted online as "Supplementary Material" for peer review.

Digital Figures. Scaling, cropping, and rotating should be performed in the originating application. We recommend Adobe Photoshop for generating pixel-based graphics and either Adobe Illustrator or Macromedia's Freehand for generating vector-based graphics. **Black and white (B/W) line art** is either pixel based (typically generated by scanning the image) or vector based (generated using a drawing program such as *Freehand or Illustrator*). Pixel-based artwork should be supplied in TIFF format and at a resolution of not less than 1,200 dots per square inch (dpi). Vector-based artwork should be supplied as EPS files. **B/W halftones** should be supplied in TIFF format. The halftone should be provided at the proper resolution. The finished resolution should be at least 300 dpi. **Color artwork** should be provided as an EPS or TIFF file. Files should be converted from RGB to CMYK. The finished resolution should be at least 300 dpi.

Note that these file formats are not acceptable for printing: JPG, PPT, GIF, ONG, PCX, PNG, XBM, Word, and Excel. We recommend creating your graphics in Photoshop, Illustrator, or Freehand and importing them into your page applications as TIFFs with all fonts included. Do not scan figures as JPEGs and convert to TIFFs.

To check the suitability of digital images for print production, authors are strongly encouraged to visit Digital Expert™ at http://dx.sheridan.com/onl/ .This free, stand-alone software application will help you to inspect and verify illustrations right on your computer.

don't publish online in the dark...

let our open linking network shed some light.

This journal is CrossRef-ed! As a scientist or scholar navigating digital content, you've come to expect dynamic linking from citation to original source. As an author, you expect ready dissemination of your work to others. CrossRef is a collaborative, cross-publisher reference linking network that allows users to click on a citation and be taken directly to the full-text location. An independent, non-profit organization that employs open standards, CrossRef was established in cooperation with leading research publishers and the International DOI Foundation. Since the service went live in 2000, CrossRef has linked millions of articles from thousands of journals. Find out more at **www.crossref.org**, and make sure all your electronically published work is CrossRef-enabled.

crossref

CROSSREF.ORG | THE CITATION LINKING BACKBONE

200 WHEELER ROAD, 6TH FLOOR, BURLINGTON, MA 01803 • 781-359-2442

Giant Resources... Purebred Content

Wiley InterScience® Reference Works

Sample Title List

Encyclopedia of Life Sciences
Encyclopedia of Statistical Sciences
Kirk-Othmer Encyclopedia of Chemical Technology
Sax's Dangerous Properties of Industrial Materials
Ullmann's Encyclopedia of Industrial Chemistry
Van Nostrand's Encyclopedia of Chemistry

Capabilities

Full text HTML and PDF (for some)
Reference linking
Citation download

Access

Single article or full title
One-time fee, subscription, or Pay-Per View options
Unlimited concurrent usage

Today's sophisticated researcher demands fast and convenient online access to the giants of scientific reference. From *Kirk-Othmer* to the *Encyclopedia of Life Sciences*, **Wiley InterScience® Reference Works** deliver the biggest names in scientific research literature to your desktop, right when you need them. Encompassing subjects ranging from chemistry, life sciences, and medicine to psychology, engineering, and physics, these multi-volume encyclopedias, handbooks, and dictionaries are enhanced by powerful functionality that accelerates your path to discovery. With **Wiley InterScience**, you can be sure to ***Discover Something Great***.

WILEY InterScience®
DISCOVER SOMETHING GREAT

WILEY
1807-2007 KNOWLEDGE FOR GENERATIONS

www.interscience.wiley.com

LEVY LIBRARY MT. SINAI MEDICAL CENTER
3 4805 0562246 5

Fresh Content Sliced Any Way You Like It

Wiley InterScience® OnlineBooks™

Content
Thousands of Wiley book titles across science, technology, medicine, business, and finance

Access
Single chapter or full title
One-time fee, subscription, or Pay-Per-View options

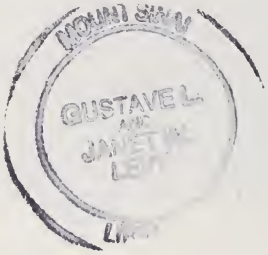
Capabilities
Search at the chapter level
Full text presented in PDF format
Citation download feature
COUNTER-compliant usage statistics

Satisfy your library's evolving research needs and budget with a customized blend of new content and licensing options at **Wiley InterScience® OnlineBooks™**. Pick and choose from an expanding roster of thousands of Wiley titles available online via **Wiley InterScience** to create a dynamic electronic book collection. Select from our new flexible licensing models – one-time fee, subscription, or Pay-Per-View. Add books as you need them from our distinguished portfolio of classic and cutting-edge titles. Whichever combination you select, enjoy unlimited concurrent access to content across the spectrum of science, medicine, technology, business, and finance.

WILEY InterScience®
DISCOVER SOMETHING GREAT

WILEY
1807-2007 KNOWLEDGE FOR GENERATIONS

www.interscience.wiley.com


GUSTAVE L.
AND

GUSTAVE L.
AND
JANET W.
LEVY

LEVY LIBRARY, MT. SINAI MEDICAL CENTER
3 4805 0562339 8